Reviewer's report

Title: No association of the polymorphisms of the frizzled-related protein gene with peak bone mineral density in Chinese nuclear families

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Reviewer: Antonio Gonzalez

Reviewer's report:

The manuscript by Gao Gao and co-workers addresses association of tagSNPs covering genetic variation in the FRZB gene with peak BMD in Han Chinese. About 400 men and 400 women are studied with their parents contributing the reference genotypes according to the QTDT approach. The subjects are young and seem not to have been selected in any defined way. Genotyping technologies and quality control seem appropriate. Analysis of data includes multiple comparisons: three phenotypes, two genders, association within families, total association, linkage and haplotype analysis. No association is found even in the uncorrected data, except for a single finding that the authors dismiss. The conclusion is that genetic polymorphisms in FRZB do not play a major role in variability of BMD among Chinese in spite of its role in the WNT pathway.

The report addresses a relevant matter because FRZB is a good BMD candidate but there are some questions that should be addressed.

Major Compulsory Revisions:

1. The paper has been written ignoring GWAS of osteoporosis/BMD. Specific mention of how the results compare with GWAS results for the FRZB locus is necessary.

2. The QTDT analysis requires normality of the phenotypes, which is not common for BMD in the population. This needs to be assessed and corrected if necessary.

3. Power of the study is needed. Its size is large but it seems that is not large enough to allow for discovery of genetic factors of modest effects in the O.R. = 1.2 range.

4. A better definition of the selection of probands is required. Are they a representative sample of the population? How were they selected? In the current manuscript, only their age and the exclusion criteria are provided.

Minor Compulsory Revisions:

5. The low frequency of the two FRZB nsSNPs that is commented at the end of the discussion should be given more relevance. A mention in the abstract will be appropriate. For most researchers interested in the subject, this information could be critical for the interpretation of the study because the two nsSNPs have been associated with OA susceptibility.
6. From table 2, it seems that there are systematic differences between the BMD values obtained in the two cohorts, the fathers and mother of the cohort with female probands has lower BMD values than the fathers and mother of the families with male offspring. This should be commented. It will be also interesting to know what kind of measures were used to assure that no subjects from one of the cohorts was evaluated with the DXA technology employed to analyse the other cohort.

Discretionary Revisions:
1. The study will be made more interesting by studying the BMD-associated LRP5 SNPs and the possible interaction between the two loci.
2. Power of the study could be increased by incorporating phenotypes of the parents in the analysis. They are available and reported in table 2. Several approaches have been suggested in the literature.

Level of interest: An article whose findings are important to those with closely related research interests

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 interests