Reviewer’s report

Title: An intron polymorphism of fibronectin gene is associated with end-stage osteoarthritis in a Han Chinese population: two-stage case-control study

Version: 1 Date: 6 December 2013

Reviewer: Evangelos Evangelou

Reviewer’s report:

Major Compulsory Revisions

1. The authors are referring to their design as a two-stage case-control study however this could be misleading. The term is used to describe techniques that intuitively are extensions of simple case-control designs to more strata. Here the authors have performed an association analysis to two independent case-controls studies and they have present a combined summary effect. Thus I would suggest removing the term throughout the text. Also, as it seems that the researchers have genotyped alla 14 SNPs in both case-control sets the discussion in the first paragraph starting at “The two stage design...not included in the tag-SNP set’ and the included reference are irrelevant to current design and should be removed.

2. The authors do not describe sufficiently how the combine the results from the two independent cohorts to provide the summary effect size and pvalue. They may have performed a meta-analysis of the effect sizes, an individual participant level meta-analysis (those methods would be helpful to indentify heterogeneity between studies as well) or they have simply pooled all available data together? This should be described clearly in the methods section.

3. It would be better to present table 2 as table 4 for consistency. It is also weird that the the effect estimates of 1.26 and 1.30 for rs940739 yield a combined crude OR (table 3) of 1.31. I suspect this due to adjustments in the second study, however this could be confusing for the reader. Also, I would strongly suggest the authors to focus the per-allele association which is far more powerful from the comparison that they have now adopted. Also, for other significant associations it would useful to state in the discussion that they do not survive a bonferroni correction for the multiple testing (n=14 SNPs)

Minor Essential Revisions

4. Recent GWAS studies have shown that different variants may be susceptible for different forms of OA. Therefore the authors should make clear in the title and in the abstract the type of OA that they are investigating which in this case is knee OA.

5. There is evidence in genetics of OA that some of the identified variants may be sex-specific. Reporting of estimates separately for men and women could be informative, even though underpowered in this study.

6. There are several GWAs published in the field for European populations.
(treatOA and arcOGEN consortia) and it might be of interest to check the strength of the reported associations in those populations. This could provide some evidence if the identified variant is ethnic-specific

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

**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