Author's response to reviews

Title: Allelic variants of IL1R1 gene associate with severe hand osteoarthritis

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Author's response to reviews: see over
Dear Editor,

We wish to thank the editors and the reviewers for the careful review and important comments concerning our revised manuscript “Allelic variants of IL1R1 gene associate with severe hand osteoarthritis” (MS: 1200836953248454). We have further revised the manuscript to improve it according to the reviewers’ comments. Please find below the detailed replies to the comments of the reviewers.

Sincerely,
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Point-by-point response to the concerns raised by the reviewers

Referee 1

The study is a good one but not so powerful. The best way to resolve the problem is to amplify the case number.

We agree with the referee that a larger study sample would have benefited this study. We feel that we have genuinely brought out this shortage in the manuscript. The study sample is family-based and selected using extreme criteria for hand OA, and thus a rare sample set and extending it within the current time line is unfeasible. IL1R1 is an excellent biological candidate for OA and we hoped to publish the results and let independent research teams to replicate the finding. However, as shown in the manuscript a large case-control cohort would be needed for the further validation.
Referee 2
Minor essential revisions:

- There are 12 e-mail addresses provided but only 10 (co)-authors on the manuscript.
  We appreciate this note, the mistake has been corrected.

- The authors have now added a figure displaying the D' measure of linkage disequilibrium but in the text of the result section r2 is provided only.
  This is a good point, the D’ values are now presented in the text as well.

- Page 10 final paragraph, it is stated : D'> xx ?
  We thank for this note, the mistake has now been corrected.

- Please provide in Table 3 the comparison that accompanies the P value.
  This is a good point, the p-values are now provided in the table.

- Please explain in the materials and methods or results section what X denotes.
  It may be not clear to the general reader that it represents the remaining haplotypes.
  We have now clarified the meaning of the “X” in the text in page 12 to make sure that the meaning of it is clear to the general reader.

Referee 3

I now noted that the current association analyses have been carried out on the sample in which the original linkage signal was found. This would allow to conduct a test in which both linkage and association are modeled simultaneously, and provides information on whether the SNPs in the IL1R1 gene explain all or most of the linkage signal (see e.g. Combined linkage and association sib-pair analysis for quantitative traits. Fulker DW, Cherny SS, Sham PC, Hewitt JK. Am J Hum Genet. 1999 Jan;64(1):259-67.). For example, if the linkage signal is no longer present after the effects of the IL1R1 gene have been taken into account, the IL1R1 gene explains all of the linkage signal. Alternatively, the outcome may point in the direction of the need to look for additional genes in the 2q area.

This was a good point and results of the analysis using GIST program has now been added to the manuscript. The program can be used to test if a marker can account in part for the linkage signal in its region.