Reviewer’s report

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

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Reviewer: danielle posthuma

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In this study six genes are evaluated for their importance in osteoarthritis (OA) using a sample of 107 familial hand OA cases, 113 primary knee cases and 536 population based controls. The genes were selected based on previous candidate gene and genome wide linkage studies. Significant association is found between the IL1R1 and OA. The rationale of the paper is set out nicely, the applied methodology is appropriate, and the results justify the conclusions. I do have some concerns about the sample size and lack of replication sample(s). Below are my pointwise remarks.

1. The sample size is relatively small compared to similar studies with other phenotypes, resulting in low power in some cases (see also p. 10). This small sample size is probably due to the nature of the phenotype. Increasing the sample size in due time may not be an option. However, searching for replication samples might be an option. Replication will certainly add to confirming this gene’s importance in OA.

2. As the most significant association is with a SNP in the intron of the IL1R1 gene, this study is not directly informative to the possible functional impact of this gene on OA. I would suggest to add a second step in this study in which functional SNPs (if known) are also included.

Minor

3. In the methods section it is stated that HWE and Mendelian errors were checked - please provide details (i.e. how many Mendelian errors etc).

4. In some sentences a couple of words seem to be missing or are misplaced, for example in the abstract, last sentence, before 'known' you probably want to add 'a'; in the introduction, last sentence of 1st para: "There is a strong genetic effects on hand and knee OA heritability..." should be "There is a strong genetic effect on hand and knee OA, with heritability..." I have not collected all instances, but please read the paper critically

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

Quality of written English: Needs some language corrections before being published
**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