Reviewer's report

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

Version: 1 Date: 6 March 2009

Reviewer: Ingrid Meulenbelt

Reviewer's report:

The paper “Allelic variants of the IL1R1 gene associated with severe hand OA” describes the genetic association of 32 SNPs in 470 kb region comprising of six genes belonging to the interleukin 1 superfamily. In total 107 subjects with severe familial hand OA and 113 bilateral primary knee OA cases and controls (N=436) were used. The questions posed by the authors are well defined and the the methods used were appropriate and well described.

The results are clearly described and the discussion assesses major drawbacks. The most important one (as recognized by the authors) is the low number of cases as compared to the number of SNPs measured which is affecting the robustness of the result. The authors argue that given the fact that their cases had unique characteristics (familial dependencies, show also linkage to the region and show significant association with the Pseudomarker program) that could overcome this problem which in part may be true. Results remain significant also considering multiple tests with IL1R1 genetic variation and hand OA.

• Major Compulsory Revisions
None observed
• Minor Essential Revisions
1. Page 10 line 17, it is very difficult to interpreter the linkage disequilibrium with the R2 measure as it indicates the redundancies of the SNPs. Please provide D’ as measure of LD.

2. Page 11 second paragraph it is stated in the first line of the second paragraph that allelic association is performed. Yet in the final sentence it is stated that a carrier risk is shown? This is confusing. It is also not completely clear to me what reference genotype is used (22 or 12).

3. The rationale of the haplotype analyses is not stated. It could either be a) SNP rs1465325 is the most important SNP since this SNP is tagging the haplotype. Then it would be worthwhile/logical to mention the genotypic OR of this SNP or b) The haplotype analyses actually break downs the effect of the SNP rs2287047 towards haplotype 3 and 5 (haplotype 5 is also showing a protective effect). In this case it would be more likely to provide the OR of rs2287047. Given the fact that the association of rs2287047 alone has the lowest P-value, option b may be most likely as recognized by the authors only mentioning the effect of rs2287047 in the abstract?
4. There is quite a difference between the P-value of the Chi2 test and the Pseudomarker program. Could it be that there is one particular family contributing to the observed association?

5. Table 3 Please provide rs numbers and order of the SNPs making the haplotypes.

• Discretionary Revisions

6. Please discuss the fact that the minor haplotype (TAAAG) shows (if anything) a protective effect in hand OA cases whereas a predisposing effect in knee.

**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 interest