Reviewer's report

Title: Allelic expression analysis of the osteoarthritis susceptibility locus that maps to MICAL3

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Reviewer: Julia Pinsonneault

Reviewer's report:

Summary

I have once again reviewed the recently resubmitted manuscript “Allelic expression analysis of the osteoarthritis susceptibility locus that maps to MICAL3” by the authors Madhushika Ratnayake, Louis N. Reynard, Emma V.A. Raine, Mauro Santibanez-Koref and John Loughlin.

As I said earlier, this study is straightforward with a simple hypothesis: The previously determined GWAS association of the minor allele of a SNP (rs2277831) to OA may be due to altered expression of one of three genes located in the vicinity of the rs2277831 locus (MICAL3, BCL2L13 and BID). The authors tested that hypothesis first by quantitatively measuring mRNA expression of the three genes in each subject and comparing normalized cycle thresholds with genotype of the rs2277831 SNP. Secondly, they measured allelic expression of the three genes, testing any allelic expression imbalance (AEI) with genotype of rs2277831 for correlation. If the authors’ hypothesis was correct then subjects with AEI in at least one of the three tested genes would correlate with heterozygosity of rs2277831.

Using joint tissue from 33 patients who had elective joint replacements (an increase from 20 in the previous submission), the authors measured quantitative mRNA and AEI in all three genes, with several marker SNPs in BCL2L13 and MICAL3. Quantitative gene expression did not correlate with rs2277831 genotype. AEI was detected in all tested genes but it also failed to correlate with SNP rs2277831 genotype. The authors concluded that their original hypothesis is incorrect. The minor allele of rs2277831 is not associated with altered expression of MICAL3, BCL2L13 or BID, and therefore the association with OA is most likely due to some other unknown mechanism. I stand by my previous comments that the authors’ study was well planned, well carried out and controlled. The manuscript is improved since the last submission. I appreciate the addition of text pertaining to splicing isoforms of BCL2L13. The manuscript is clear, well written and easy to follow. The overall conclusion of this study, being negative, is still not very compelling. The addition of new subjects serves to strengthen that conclusion. It is nevertheless important that negative results like these be published.

Major Compulsory Revisions:

None
Minor Essential Revisions: None
Discretionary Revisions: None

**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.