Reviewer's report

Title: Genome-wide analysis of aberrant methylation of enhancer DNA in human osteoarthritis

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Reviewer: Mohammad Reza Jabal Ameli Forooshani

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Lin et al. carried out a genome-wide DNA methylation analysis across 108 methylation profiles ascertained from osteoarthritic patients and healthy controls. Through the application of different bioinformatics approaches, they determined differentially methylated (DMT) sites across two osteoarthritides (OA) subtypes (knee and hip) and different genders. They identified 8,111 DMT enhancer regions and showed that 84.5% of CpGs are hypomethylated among hip specimens collected from female patients. Using PCA and hierarchical clustering, they showed that methylation profile for knee and hip OA patients is distinctly different across the age ranges (55-88 y/o). Overall, the authors deliver a clear message; nevertheless, I have a few comments:

The first and most important concern is about the originality of the research. While authors acknowledge that they re-used the methylome data from an earlier study by Rushton et al., 2014 in the method section, they do not explain how their result is different from the earlier study and what new insights their analysis provides. Moreover, the abstract and background section need to reflect clearly that methylome data is retrieved from the GEO, and the authors did not generate the data through the course of this study.

Despite the sharp and grammatically flawless abstract, the main body of the article requires meticulous grammatical editing. Also, the gene IDs should be italicized in the text (e.g. COL11A2).

In the second paragraph, when authors introduce methylation as a form of epigenetic changes, they are encouraged to briefly describe the chemical modifications at the single nucleotide level and emphasize that methylation is influenced by lifestyle and environmental factors and vary across the life course.

Occasionally, the authors failed to provide the relevant reference when they referred to previous studies. For example, lines 35-41 in the "background" section or lines 21-24 in the section describing "Classification of enhancer probes".

Did the authors use one-way t-test or two-way t-test for pair comparison of methylation differences between two groups?

Please consider adding the significance threshold lines for the figures showing GO enrichment results. In figure 3.A, it would be interesting to see where the "three male patients" cluster across the group-1.

Taken together, given authors provide a satisfactory explanation for the major concern set above and adequately address the minor points, I recommend the paper for publication.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Needs some language corrections before being published

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