**Reviewer’s report**

**Title:** Association of Catechol-O-Methyltransferase Single Nucleotide Polymorphisms, Ethnicity, and Sex in a Large Cohort of Fibromyalgia Patients

**Version:** 0  **Date:** 29 Jan 2018

**Reviewer:** Wei Yang

**Reviewer's report:**

This is a large-scale multi-racial association study of the mutations in the COMT gene with Fibromyalgia. I appreciate the great effort by the authors to carry out such an extensive study. However, I have great concerns about the study design and how racial differences have been handled when statistical analyses were performed.

More specially,

(1) How representative are the control samples?

(1i) The control samples seemed recruited from clinical visits. It is possible that they have very different compositions with regard to genetic variations, gender, ethnicity compared to the general population, and may lead to many of the differences observed in the current manuscript.

(1ii) The manuscript compared the allele frequencies between FM group and the 1000 genome data. I wonder why the comparisons have not been performed to compare the non-FM group to the 1000 genome data to see how the controls samples compares to the general population.

(1iii) Page 8 line 35, I don't think diagnosis rate could be directly derived if the controls samples were not recruited from general populations. In the same paragraph, "Only those participants with genetics for the COMT single nucleotide polymorphisms… were included in the downstream analysis". What is the criteria that sample have been selected for genotyping? This could affect the distributions of sex, race, and genetical variations, also.

(1iv) Page 11 line 24-25: "The FM group was compared of 71.6% females compared with 58.5% females in the non-FM group". Does the general population has female make up as high as 58.5%?

(2) In genetic association studies, the allele frequencies and effect of mutations generally show distinct differences across racial groups. Many statistical tests seem having been performed without consideration of the racial difference.
(2i) What is the frequencies of the haplotypes in each race group? Is there any difference in haplotype distribution across race groups? Is there any difference between FM and non-FM samples within each race group?

(2ii) Table1 showed allele frequency difference across all race groups. This could be meaningless considering the generally huge difference between race groups, and the male:female compositions are different in FM and 1000 genomes data.

(2iii) Also in Table1, for SNPs that showed different MAFs between sexes, the difference might be driven by the difference in sex compositions.

(3) Page 6 the last paragraph. Is the "sympathetic" nervous system or the "autonomic" nervous system the identified in the pathogenesis of FM? Page 7 Line 1 says that "The autonomic nervous system likely plays a role in regulation of fibromyalgia pain, as functional MRIs in FM subjects with higher levels of sympathetic nervous system activity demonstrated more temporal summation of pain". I am not able to see the logic in this sentence, how "higher levels of sympathetic nervous system" relates to the role of autonomic nervous system?

(4) Page 12 line 22-29: "there was an association of COMT diplotypes when stratified by ethnicity: African American were 11.3 times more likely to have … than Caucasians". This is comparing the African American samples to the Caucasian samples, not "stratified" analysis by ethnicity. The latter means analyses performed within each ethnical group.

**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.

Unable to assess

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

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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