Author’s response to reviews

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

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Author’s response to reviews:

Dear Reviewers,

Thank you very much for your thoughtful feedback. We have implemented the suggested changes and the paper is improved as a result. We appreciated the opportunity to revise this manuscript.

Thank you,

Ashley Brenton, PhD
Technical Comments:

Editor Comments:

The reviewers acknowledge that the manuscript has been improved. However, there are still some essential details (in particular regarding the description of the non-FM group) that have to be addressed properly before the manuscript can be accepted for publication.

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Reviewer reports:

Jacob Ablin (Reviewer 1): no further comments.

Andrea G Nackley, PhD (Reviewer 2): The manuscript has been improved. Remaining concerns are indicated below.

Major Concern:

There is still a concern that demographic risk factor analysis compares FM and non-FM groups, while genetic risk factor analysis compares FM and 1000 genomes groups. The authors state, "The non-FM participants were recruited in a similar fashion as the FM participants. However, we acknowledge that because participants were recruited from doctor visits, mainly in offices that deal with pain, our non-FM sample is skewed toward those who are sicker and/or also have chronic pain conditions."

(a) In the Methods section, authors state that non-FM participants were identified as those not diagnosed with FM that were further filtered to exclude conditions comorbid with FM (eg, OA and TMD) as well as chronic conditions and pain diagnoses. This does not fit with the response above. More information- specific details need to be shared regarding the non-FM group.
When patients visit doctor’s offices, for billing purposes, services performed for that visit will be given diagnoses codes. Our knowledge of their conditions is limited to what is in their medical records for those visits. If they were visiting for an acute condition, for example, but have an underlying chronic condition that was not the reason for the visit, the acute condition will show up in their medical records but the chronic one would not as that was not the reason for the visit. If the undocumented chronic condition was fibromyalgia, we would miss them in our filtering since we have no record of them having fibromyalgia. We did not have any other diagnoses related information about patients prior to the study. We did add a disclaimer in the discussion that a better study would have a clearly defined control group.

(b) If the non-FM group includes an ambiguous group of individuals, some of whom have chronic pain conditions that possibly overlap with FM (other than OA and TMD), then interpretation of demographic findings is compromised.

We understand that our filtering may have missed someone (as explained above) with FM. We make the assumption that our misclassification rate is not high enough to drown out signal in the data. If our misclassification (into FM and non-FM) were high, we should not have seen any demographic differences as we did not filter for any demographics, only diagnoses.

(c) On the other hand, if the pain status / chronic pain condition diagnosis is known for members of the non-FM group, then a direct comparison of painful FM vs painful other conditions (which might pare down the N from the total non-FM group) might provide useful demographic and genetic markers specific for FM vs other pain conditions.

You are also correct in that FM vs other pain conditions would be a great study setup. Unfortunately, in this study, we did not design the non-FM group to be just one specific pain condition. There is a mix of conditions in that group. The best we could do was to filter for conditions that we knew to be comorbid with FM.

Minor Concern:

In the Abstract, authors now clarify that females between 49-63 years are at higher risk of FM. Then they go on to note that low and mid age groups have increased odds of FM after adjusting for sex and ethnicity. The terms 'low' and 'mid' have not been defined for the reader to be able to interpret. The age tertiles need to be defined in the Methods section of the Abstract.
We do explain the limits of the tertiles in the Methods section of the paper: “age was re-categorized by tertile: low (<49), mid (49-63), and high (>63).” We have added it to the abstract as well.

Wei Yang (Reviewer 3): Some of my previous points have been adequately explained/addressed. Below are some that still need attention:

1. When describing the non FM samples, it would be helpful to make it clear that "Subjects were recruited from physician offices and were included in the study only if the physician deemed the genetic test was medically necessary to assess risk of FM."

Thank you for the suggestion. We have added it under “study participants” under the methods section.

2. Table 3. Two of the 4 SNPs showed constant change in the FM group across race and gender groups. These are compelling evidences of association. However, for the other two SNPs, rs6269 showed opposite directions in African Americans and Caucasians; In females, rs4818 shows contradictory changes in the combined samples compared to the African American group. In presence of obvious heterogeneity, the test when comparing across race/gender groups should be performed with this in consideration. I would recommend using tests such as "stratified" analysis instead of direct test for frequency difference. Also, it might help to include an extra column to show the estimated effect size, such as odds ratio, so that even when a comparison is not statically significant probably because of small sample sizes, we would see how the effect size compares to the other groups.

Thank you for this suggestion. As p-values are dependent on sample size, in general, we think the extremeness of the p-value can be used as an indicator of effect size. We look forward to conducting more in-depth analyses to expand on some of these findings in a larger sample size.

3. When describing the results for diplotype associations: "there was an association of diplotypes when analyzed by ethnicity”. This is not an association with race groups, not with FM. It shows nothing but ethical differences. I recommend revision to avoid confusion.

We believe the reviewer is referring to this sentence:

“While there were no statistically significant associations of COMT haplotypes or diplotypes with FM diagnosis in the FM group compared to the non-FM group, there was an association of COMT diplotypes when analyzed by ethnicity: African-Americans were 11.3 times more likely
to have COMT diplotype corresponding with high pain sensitivity than Caucasians, regardless of whether or not they were diagnosed with FM (p=7.27 x 10-249; Figure 2).”

The underlined portion states the result was because of ethnicity differences not FM.

We’ve changed the sentence to this:

“There were no statistically significant associations of COMT haplotypes or diplotypes with FM diagnosis in the FM group compared to the non-FM group. However, when only ethnicity was considered, there was an association of COMT diplotypes: African-Americans were 11.3 times more likely to have COMT diplotype corresponding with high pain sensitivity than Caucasians, regardless of whether or not they were diagnosed with FM (p=7.27 x 10-249; Figure 2).”

4. Some descriptions regarding "controls" should be made clear whether it refers to the non-FM samples or the 1000 genome data. One examples is the first paragraph in the discussions: "Our study demonstrates the minor alleles of rs4680 occurs in higher frequency in FM subjects compare with controls".

Thank you for the catch, we have updated that sentence in the discussion.