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 Editor and Reviewers,

Thank you very much for your suggestions. We have incorporated these suggestions into the manuscript and appreciate the opportunity to revise and improve the manuscript.

Best,

Ashley Brenton
Editor Comments:

BMC Rheumatology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Andrea G Nackley, PhD (Reviewer 2): In the Discussion, the authors now state, "Additionally, a clearly defined group of individuals without FM or comorbidities, such as chronic pain, would serve as a more definitive control for the FM group." Prior to this sentence, the authors need clarify that it is possible that participants with FM or another chronic pain condition who were seen for an acute condition, might have been included in the control group.

Thank you for this suggestion. We have updated the manuscript.

Wei Yang (Reviewer 3): Remaining concerns are indicated below.

For my previous comment 3 on using statistical tests with consideration of heterogeneity effect and on suggestion to show effect size. I believe the authors have misunderstanding on statistical significance and effect size. This reference might be helpful for better understanding: Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. Journal of graduate medical education. 2012 Sep;4(3):279-82.

With regard to the recommendation of using "stratified analysis" for rs6269 and rs4818, instead of simply pooling samples across heterogeneous groups, it is statistically more sound to pool the association results across groups. This is not additional "in-depth" analysis, but using statistics the right way.

We do not fully understand what the reviewer is asking for when referring to “With regard to the recommendation of using "stratified analysis" for rs6269 and rs4818, instead of simply pooling samples across heterogeneous groups, it is statistically more sound to pool the association results across groups.” We think the reviewer would benefit from a review of our approach, so we will clarify the two comparison we did in this study, what tests we used and why.

FM vs Non-FM – this was a comparison of patients in our study, the FM group (n=2,713) had clinically diagnosed fibromyalgia and the non-FM group (n=32,141) did not (and, also, did not have other FM comorbidities). For this comparison, we clearly stated that we used a logistic
regression model with sex, ethnicity and age as covariates. The model coefficients, which is also known as “effect size,” are reported in table 2, along with their p-values, and figure 1 shows the distribution of each covariate. We stated that in this comparison, we found no association with FM and the COMT SNPs nor with the COMT diplotypes (figure 2) even after adjusting for sex, ethnicity and age. The logistic regression models used in this comparison pools p-values and reports coefficients/effect size across all groups.

FM vs 1000 Genomes (1000G) – this was a comparison of the minor allele frequencies of each COMT SNP. Because the sample size in the 1000G group was very small, it is not appropriate to use the logistic regression modelling that we implemented in the FM vs Non-FM comparison. The goal of the 1000G project was to get population estimates for various MAFs for different ethnicities and sex. Thus the question we sought to answer was, “Do the MAFs of our FM group significantly differ from the population estimates?” A simple test of proportions was appropriate because of (1) the small sample size of 1000G, and (2) we were only interested in if the FM MAFs were significantly different from the population. The effect size in this model is just the difference between the FM MAFs and the 1000G MAFs.

For previous comment 4, the following change has been made "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 ..." Within the context of studying the association of between genetic factors and FM diagnosis, simply state there is an association could easily be misunderstood as an association with the FM diagnosis. It is worth making clear by, for example, changing to "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 with ethnicity groups"

Thank you for the suggestion, we agree that this is a clearly wording. The manuscript has been updated.