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: 11 Dec 2017

Reviewer: Andrea Nackley

Reviewer's report:

Here, the authors conducted a retrospective analysis of demographic and genetic data collected from FM and non-FM controls to determine factors predictive of FM. Additional data from 1000 genomes was included for genetic analysis. Overall, the manuscript is well-written and data interesting. However, the methods lack rigor and the findings lack novelty. Specific concerns are indicated below.

Major Concerns:

1. Demographic risk factor analysis compares FM and non-FM groups, while genetic risk factor analysis compares FM and 1000 genomes groups. COMT SNP minor allele frequencies need to be reported for the non-FM controls as well as the FM and 1000 Genome subjects. Risk predictions should include genotypes of non-FM participants that were recruited in a similar fashion to the FM participants. The non-FM group also has age information that would be important to control for in genetic analysis.

2. The chi-square analysis showing risk allele frequency for each COMT SNP is interesting from a descriptive standpoint, but not rigorous in terms of establishing an association of SNPs with FM. Logistic regression models should be used to determine the relationship between SNPs and case status, while including age/sex/ethnicity as covariates in order to show the independent contribution of each COMT SNP.

3. When looking at the relationship between ethnicity and FM risk, age group and sex were adjusted. Was the relationship between age and FM and sex and FM also evaluated while adjusting for other factors?

4. The manuscript is well-written overall, but lacks cohesion. All sections, including the methods, results and figures, and discussion should be presented in a logical order that parallels the abstract. Demographic data should be presented first, followed by demographic risk factors, then genetic factors. Suggested order should be:
5. In the Introduction, the authors note that serotonin and catecholamines are key neurotransmitters in pain-inhibiting pathways. This is not entirely accurate and is counter to the premise of the current study. Catecholamines are known to either initiate or inhibit pain based on the cell type and context surrounding their expression. The premise for the current study is based on the idea that COMT SNPs associated with low activity (leading to increased levels catecholamines) are predictive of painful FM. The authors can refer to and cite the Smith et al., Pain, 2014 paper that examined these COMT SNPs and haplotypes for association with COMT activity levels.

6. The authors conclude that, based on their descriptive genetic findings, COMT activity and catecholamines are not likely driving the development of FM pain. There are many factors that influence COMT expression/activity and catecholamine bioavailability, so this is a very big assumption to make. Then it seems contradictory that COMT genetic variants associated with low activity are more prevalent in African-Americans who are at greater risk for FM.

Minor Concerns:

1. In the Abstract, authors state, "Females, younger individuals, and non-Caucasians were at higher risk…" As both the 'low' and 'middle' age groups were predictive of increased risk, it would be helpful to specify the age. The middle age group ranges 49-63 years, so the term "younger individuals" is misleading. Then in the Results section, Table 3 and Figure 2 suggest that the middle age groups are at greater risk. Please present findings and interpretation of findings in a consistent manner.

2. In the Abstract, present the results in a consistently ordered way. Move the 2 African-American and Hispanic race results up a sentence, so as to follow the "Females had 1.72 increased odds…" sentence.
3. In the Abstract Conclusions, "This is the largest study to date that examines…” should be "This is the largest study, to date, that examines…”

4. The sentence in the Introduction, "Although criteria to diagnose FM exist, specifically a number of widespread painful tender points [9], solidifying the diagnosis is tricky since other presenting symptoms and comorbid diseases are likely to exist." does not clearly specify criteria for FM diagnosis. The criteria have changed over the past several years. Are you referring to the widely-used 1990 criteria (requiring presence of pain upon pressure applied to at least 11 of 18 specific points), or the updated 2010 criteria (that no longer use these tender points)?

The fact that the criteria for FM are subject to change, might even provide a compelling argument for an objective genetic biomarker.

5. Also, replace "tricky" with a synonym such as "challenging."

6. In the Methods, authors note that only participants with genetic data for COMT SNPs were included in the analysis. Is this a subset of the 2,713 FM and 32,141 non-FM groups? Then, in the Statistical Analysis section the authors note the FM group was compared to individuals in the 1000 Genomes Project from US population (n=224). Does the 224 refer to those from the 1000 Genomes? Please clarify the exact number of FM, non-FM, and 1000 Genome subjects used for the analysis. This information is in Figure 2, but needs to be clear in the text.

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.

No

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

No
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