Reviewer's report

Title: Associations between genetic polymorphisms and temporomandibular joint disorder

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Reviewer: Susan Armijo-Olivo

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Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

Title:

the term: “temporomandibular joint disorder” should be replaced for “temporomandibular disorders”. The term “temporomandibular joint disorder” is an old term and has been replaced by the term suggested. Also I would suggest creating a title that is reflecting the results of the study and more attractive.

A. Abstract:

Background and objective: No clearly stated which the objectives and the need for the study were. Please clarify.

Methods: “After obtaining the data, a chi-square test was performed to evaluate the different frequencies of the alleles and genotypes in the TMD patients and healthy controls.” Do you want to say that a chi-square test was used to determine the differences in proportions of subjects exhibiting alleles and genotypes between TMD patients and healthy subjects? If yes, statistical methods should be reworded. It does not read very well.

Results: six of the polymorphisms (......) showed “significant?” associations with TMD. It is not clear to me when the authors stated the following: “exhibiting significant changes in their allele and genotype frequencies”. Could you please clarify this sentence?

I would delete the sentence: “However, in other studies, other polymorphisms, such as ESR1 (rs9340799/rs2234693) and SLC6A4 (5-HTTLPR), did not show associations.” This is part of discussion. Generally, it is not used as part of abstract.

Conclusions: The results should make a link with the conclusions regarding the polymorphisms. It seems that conclusion is not connected with the results and it looks odd the way it is right now. Maybe in the results part you should add a little bit that these polymorphisms are related to inflammatory oxidative stress and neurotransmission responses to pain for example.

B. INTRODUCTION:
1. I would add that TMD is commonly associated with other related-symptoms in the head and neck. Please add more information specifically to TMD and their importance.

2. Regarding the causes of TMD, there is a long list of factors that are questionably linked with TMD. I would suggest to authors adding that information since the causes of TMD are still a matter of a lot of debate and also to point out that a multifactorial origin might be plausible.

3. Regarding the statement: “it is assumed that a combination of factors related to environmental and/or nutritional stress”. Could you please provide examples of environmental and nutritional stress? Also this statement needs references.

4. When talking about genetics, could you please expand more on that since this is the essence of the paper and explain what type of genetics variants are present in TMD?

5. The following paragraph is odd and does not contribute in any aspect to the introduction. I would delete it or complemented with information linked to the previous topic: “The cells are influenced by genes and environmental conditions at the time they migrate, proliferate, differentiate, and synthesize the extracellular matrix in specific directions and magnitudes, finally resulting in macroscopic forms, such as the condylar aspect. Mechanical forces, therefore, modulate bone and cartilage growth”

6. Is the question posed by the authors well defined?

   1. The authors need to clearly state what is (are) the objective(s) of this study and also why did the study these specific polymorphisms. There is no clear statement of why this study needs to be done. It is kind of vague information; however, the link is not explicit.

C.METHODS

1. The recruitment and details of participants selection would be easier to understand if a flowchart would be added.

2. There are some inconsistencies in the English grammar in the first part of the methods section: For example: “14 because they were not come to the physical examination and 33 because they were not confirmed clinical signs of TMD”. Do you want to say that “14 subjects were excluded because they could not come to the physical examination and 33 had not clinical signs of TMD”. Please revise the grammar throughout the manuscript and correct the misspelling and these odd sentences.

3. I recommend not using the expression: “responded positively or negatively”. You should say : “subjects were diagnosed as having/ no having TMD based on RDC/TMD criteria”

4. was there any sample size calculation to determine the sample size needed prior data collection

5. It is recommendable to add information regarding data collection and assessment:
a. Who screened the subjects for inclusion? Could you please clarify that?
b. Where subjects with TMD classified in different groups (i.e. myogenous, mixed, or according to the categories specified by the RDC/TMD?)
c. How was the evaluation performed?
d. Was any inclusion/exclusion criteria?

6. The authors stated: “The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) outlined by the International RDC/TMD Consortium were used as a diagnostic tool and the inclusion-exclusion criteria”. The RDC/TMD is a method to evaluate and diagnose TMD. I am not sure how the authors used as inclusion/exclusion criteria.

7. The authors presented the demographics as a text. I would prefer them to be presented in a table.

8. How control subjects were screened? What were the inclusion criteria for them?

9. Technique for genotyping: Please provide information regarding validity and reliability of the technique and software used to determine the outcomes for the study. Please provide references.

D. STATISTICS

1. I would recommend revising and rewording the statistics part of the manuscript. As a suggestion, please link the objectives of the study with the statistics performed.

2. The statistics are very general and do not provide clear information of the analysis. Authors should be more precise in determining variables and different analyses.

3. How they calculated Odds ratios. Do they provide crude Odds ratio? What method was used?

4. Why Odds ratios were only calculated for only some comparisons?

5. It seems that many associations were done by using chi-square test. Why the authors did not calculate the odds ratio adjusting for some other variables such as gender, age, etc.

6. I would recommend consulting with a statistician.

E. RESULTS

1. I am not sure if Figure 1 is needed. There is no major explanation of it.

2. Please revise the writing in results part. Results are reported too general and it is difficult to follow. Some sentences are cut or the idea is not clearly finished. For example: “From the four polymorphisms studied on the cytoplasmic Serine Hidroximetil Transferase 1 gene (SHMT1) in TMD patients, a significant increase (p<0.01; OR=3.99) was observed of the G allele (LEU) of the polymorphism rs1979277 (LEU435PHE)”. When compared with healthy subjects?

3. Please be more specific when reporting numbers in text. Please provide
estimates and frequencies and 95%CI and exact p value. So, it is easier to understand where the results came from.

4. Do not report “p” significance value in isolation. This is not helpful for readers.

F. DISCUSSION

1. I would add more information regarding the importance of genetics factors in TMD. Authors just mentioned it but they do not expand on it.

2. The authors mentioned: “The folate-methionine axis takes part in both factors because in this axis”. Could you please clarify which factors are you referring to?

3. Please check the coherence of paragraph 2 of discussion with previous and following one. Not sure what they are trying to say

4. when talking about higher frequency (please provide the number) 4rd paragraph discussion: “In our case, a higher frequency of the allele SHMT-rs1979277G was observed in TMD patients”

5. There are many sentences in the discussion without references. I would recommend adding the backup for those statements.

6. Discussion, paragraph 8, “Regarding previously studied polymorphisms, in which associations with TMD…” please expand the results from other studies and controversies regarding genetic studies. This paragraph should be expanded to express better the idea.

7. Please address the limitations of this study

8. Please provide a more refine discussion, addressing points that are directed to the objectives of the study. I find the discussion a little bit vague.

G. CONCLUSIONS

The conclusion is not very clear. Maybe something is missing?

Please relate the conclusions to objectives

H. REFERENCES

There are some references that are not in a good format. Please check them again and follow the journal guidelines to format references.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. Please locate references after punctuation

2. after a period, numbers should be written in letters, no numbers

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Grammar and writing style should be revised

2. Table 2 needs to stand alone. What do the numbers in parenthesis mean?
Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests