RESPONSE TO REVIEWERS:

We have taken into account the valuable suggestions that the reviewers made on our manuscript. Overall, we improved the section of Patients and Methods adding important details that were missing in the first draft and organizing it to make it clearer. In addition, we highlighted the most relevant findings and the clinical implications of our study.

Reviewer reports:

Reviewer #1: Language review - excellent

Overall, this is an exceedingly good study, very well written and comprehensive

Reviewer #2: language: well written

Introduction:

1. Please describe the gold standard in diagnosis (genetic testing); you could use Swillen et al. 2015, Developmental trajectories in 22q11.2 deletion and /or Orpha.net as reference.

We have included the standard in diagnosis as follows:

“The diagnosis of patients with 22q11.2DS is suspected in individuals with cardiac defects or vertebral anomalies, which is confirmed if the deletion is identified by using FISH, MLPA, aCGH or CMA...
2. What is the genetic inheritance pattern if a patient is affected?
3. It might be advisable to mention that a high percentage is caused by de novo mutation. We have included these suggestions as follows:
   “and with above 90% of cases being the result of de novo mutations during early fetal development and some of them inherited in an autosomal dominant pattern”

Patients and methods: 4. Did you screen the patients for palatal abnormalities especially for cleft lip palate?
5. Did you exclude cleft lip palate patients? If not, you should mention this in the discussion because facial aberrations could result from this condition.

We have made these points clearer as follows: “The patient group included only individuals without palatal abnormalities or VPI surgery to avoid increasing facial variability due to the presence of this disorder”.

6. You mentioned the usage of your findings for clinical training. It might, therefore, be helpful to insert a table with a list of significant aberrant features for each age stage.

A table (Table 3) was compiled as requested, including data regarding the most significant clinical features found in patients by stage (G1, G2 and G3) and the manuscript text was modified accordingly, within the Results section.

Results: 7. Please clarify the section describing significant and non-significant results (especially lines 38 to 51). For example, what is meant by group status? Is this patient group vs. Control? Please highlight and emphasize your significant results. We have rewritten and expanded this section in order to clarify the findings of our study and to emphasize and highlight the significant results.

Discussion: 8. What was your decision for the separation of the age groups based on - you could mention growth studies or percentile curves for explanation?

We have made this decision clear within the Patients and methods section, as follows:
“Both groups were subdivided into different age groups that roughly reflect the major stages of development (i.e. early childhood, middle childhood, and adolescence), and, as far as possible, with balanced sample size”

9. Why did you use the fluorescent in situ hybridization instead of MLPA, aCGH or SNP micro array methods? Only monetary reasons or accuracy of the method?

We have considerable experience in the use of FISH to detect deletions at 22q11 and manage an efficient and reliable pipeline to perform that technique in terms of expertise, reagents and equipment. We did not employ MLPA as we do not have access to a fragment analysis instrument and we lack the capability to acquire the appropriate SALSA probe kits. In the same way, aCGH or SNP micro arrays were not employed, again because our lack of access to instrumentation capable to hybridize or scan such arrays. Of course, the cost of the arrays themselves is also a factor. Conclusion: 10. You should highlight that significant differences could be found. We highlighted the relevant results of our study as follows:

“We found that Mexican patients exhibited typical traits that have been reported for the Caucasian population, and that those traits differ significantly from that of controls on average and at each ontogenetic stage. In addition, we found that the developmental and allometric trajectories of patients and controls were similar, but that they differ in facial growth patterns”.

Reviewer #3:
General:
1. Very long literature review, limit to 40 relevant papers, very long literature review. We agree that it is a very long literature review; however, we considered that we have selected the most relevant literature to the content presented.
   However, some references were removed

M&M:
2. Very long and unorganized, add subheadings for study sample, study sample size calculation, variables measured, statistical analysis,
We have taken into account this suggestion by adding subheadings within the Patients and methods section.
Results:
3. Some parts of the result section (initial paragraphs) need to be relocated to M&M what are the clinical implications
We relocated some parts of the result section into the Patients and methods section as suggested.
4. Revise for grammar and style, many typos!!
Thanks for the comment, the revision of spelling errors in the manuscript is made and corrected.

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