Author's response to reviews

Title: A unique phenotype in a patient with a rare triplication of the 22q11.2 region, and new clinical insights of the 22q11.2 deletion and microduplication syndromes: a report of two cases

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Author's response to reviews: see over
Answers to Reviewer HM (Dr. Heather McDermid)

Comments    Author’s corrections

Major Compulsory Revisions

1. The Reviewer suggests that the manuscript should focus “on the triplication case, with an additional case of duplication described, and remove all data concerning the 2 deletion cases”.

We agree and revised the manuscript accordingly, changing its title, focusing on novel information related to a patient with 22q11.2 triplication, but also to a patient with duplication, and adding references 15 and 16 (please see Abstract section, page 3 lines 52-54, pages 3-4 lines 60-63; Background section, page 6 lines 96-97; Conclusions section, pages 9-10 lines 176-178 and 198-201).

2. The Reviewer mentions that “it’s important to connect the patients’ original designations in Pires et al. (2014) to the new manuscript (...) to help the future reader compile the data”. We understand the Reviewer’s point of view; however, if we had changed the patient with 22q11.2 duplication to “patient B”, and the patient with 22q11.2 triplication to “patient C”, we would also be changing the style of BMC Pediatrics’ case reports, which describe the patients as “case 1, case 2, etc” (please see Wu et al. BMC Pediatr, 2014; 14:255). In order to fulfill the Journal’s style, we designated the patient with 22q11.2 duplication as “case 1”, and the patient with 22q11.2 triplication as “case 2”.

The Reviewer also states that we “should give more information on the duplication/triplication (breakpoints) and reference Pires et al. each time information from that paper is used (especially in the case presentations)”. We agree, included the breakpoints of duplication/triplication (please see Case Presentation section, page 7 lines 129-130, and page 8 lines 155-156), and cited Pires et al. [reference 12] at appropriate places (please see Case Presentation section, page 7 line 127 and 130, and page 8 lines 152 and 154).

3. The Reviewer advises that “it is imperative that Table 1 be restructured. The two deletion patients can be removed. There should be four new columns: one that summarizes the features of all previously reported patients with a 22q11.2 microduplication syndrome (...), one that gives the features of the first case of triplication (Yobb et al.) (...) and columns for the duplication parents of the children with triplications”.

We agree that the reconstruction will make it much easier for comparison to future cases and will put the cases with duplications into better context. We proceeded accordingly, removing the two deletion patients, maintaining the patients with duplication (column “Case 1”) and triplication (column “Case 2”), and adding four new columns as follows (please see Table 1, page 16):

- The first is entitled “Other cases”, and includes all the features found in patients with 22q11.2 microduplication syndrome, according to the literature [references 2, 10, 23 and 24];
- The second is named “Father”, and includes “cognitive deficits” diagnosed to case 2’s
father, who has 22q11.2 microduplication syndrome;

- The third is entitled “Patient”, and describes the clinical features of the first reported patient with 22q11.2 triplication, according to Yobb et al. Am J Hum Genet, 2005; 76:865-876 [reference 10]; and

- The fourth is named “Mother”, and includes “hand/foot abnormality” diagnosed to the patients’ mother reported in Yobb et al [reference 10].

The Reviewer also mentions that “in the first patient with a triplication, the table in Yobb et al. indicates that the hearing defect is probably secondary to otitis media”. We appreciated this note and included this information in table’s footnote “c” (please see Table 1, page 16 line 332).

4. The Reviewer points out that the main conclusion of this manuscript, i.e. that “this genetic alteration [22q11.2 triplication] could be responsible for a variation of the 22q11.2 microduplication syndrome, with aggravated phenotype due to the major dosage of implicated genes” is not supported by the evidence, since there are only two patients with triplication in the literature, one mild and one severe.

We agree and revised the manuscript accordingly, stating that “the case 2 here described presented an aggravated phenotype in contrast to the previously reported, which has a milder phenotype. Both triplication cases fit within the 22q11.2 duplication spectrum. Some factors may contribute to their phenotypic variability, such as different genetic dosages, abnormalities in the parent of origin or imprinted chromosomal material (e.g. uniparental disomy).” (please see Conclusions section, page 10 lines 206-211).

Minor Essential Revisions

5. The Reviewer asks if we are suggesting that the Sturge-Weber syndrome is related to the presence of the triplication. We do not suggest this relationship, and clarified this point by reformulating the previous sentence to: “In fact, patient 2 presents similar features [to Sturge-Weber syndrome] (Table 1), and possibly has the somatic mutation c.548G>A (p.Arg183Gln) in the GNAQ gene.” (please see Conclusions section, page 10 lines 195-197). Moreover, in Table 1 we indicated all Sturge-Weber symptoms in patient 2, as suggested (please see footnote “b”, page 16 line 331).

The Reviewer also asks if there is any other additional phenotypic information about the patients’ affected father. We confirm that he presents cognitive deficits (please see Table 1, page 16).

6. The Reviewer states that the monozygotic twin of current case 1 is very interesting, since she presented a different cardiac defect. We agree and concluded that there are not previous cases of monozygotic twins with the 22q11.2 microdeletion syndrome and different cardiac defects, which is a major finding of our study and an additional reason to maintain this case in the manuscript (please see Abstract section, page 3 lines 53-54; Conclusions section, page 9 lines 176-178, and page 10 lines 199-201).

7. The Reviewer mentions that the abstract refers to DiGeorge syndrome (DGS) but not Velocardiofacial syndrome (VCFS), suggesting that the 22q11.2 deletion syndrome should be referred to as DGS/VCFS here and later in the paper, rather than just DGS. We agree and revised accordingly by adding this information at appropriate places (please see Abstract
Moreover, the Reviewer also advises that the description of the DGS/VCFS phenotype should include palatal defects and velopharyngeal insufficiency. We agree and proceeded accordingly (please see Abstract section, page 3 line 44; Background section, page 5 line 77).
A unique phenotype in a patient with a rare triplication of the 22q11.2 region, and new clinical insights of the 22q11.2 microduplication syndrome: a report of two cases

Answers to Reviewer SY (Dr. Shi-Hui Yu)

Comments       Author’s corrections

Major concerns

The Reviewer refers that “the three cases (patients 1-3) in this report present nothing new, both genetically and phenotypically”. We agree that patients 1 and 2 should be removed, and we proceeded accordingly. However, former patient 3 (currently case 1) is very interesting, since she presented a different cardiac defect from her deceased monozygotic twin. After review of the literature suggested by other Reviewer, we concluded that there are not previous cases of monozygotic twins with the 22q11.2 microdeletion syndrome and different cardiac defects, which is a major finding of our study and an additional reason to maintain this case in the manuscript (please see Abstract section, page 3 lines 53-54; Conclusions section, pages 9 lines 176-178, and page 10 lines 199-201).

The Reviewer points “The 22q11.2 triplication in Patient 4 is interesting. An aCGH image showing the triplicated region is necessary”. We agree that former patient 4 (currently case 2) with the triplication is interesting, and maintained it in the manuscript. This manuscript focus on clinical descriptions and provides novel information of two patients affected with 22q11.2 rearrangements that we have recently characterized using molecular techniques (Pires et al. BMC Genet, 2014; 15:115) [reference 12], a paper where is available the aCGH image showing the triplicated region. Since we do not intend to produce a duplicate publication, we cited Pires et al. [reference 12] during the description of materials and methods used in this manuscript (please see Case Presentations section, page 7 line 127 and 130, and page 8 lines 150-152).

The Reviewer mentions that is required the description of material and methods used in this report. Again, since we do not intend to produce a duplicate publication, we cited Pires et al. during the description of materials and methods used in this manuscript (please see Case Presentations section, pages 7 lines 126-127, and page 8 lines 150-152).

Minor concerns

The Reviewer refers that “There are numbers of grammatical errors in this manuscript”. We appreciated this comment and corrected these errors, following suggestions of three native English speakers (please see Acknowledgements section, page 12 lines 244-247).

Quality of written English

The Reviewer states that the manuscript “needs some language corrections before being published”. We also appreciated this comment and proceeded accordingly, following suggestions of three native English speakers (please see Acknowledgements section, page 12 lines 244-247).