Author's response to reviews

Title: Intergenerational and Intrafamilial Phenotypic Variability in 22q11.2 Deletion syndrome Subjects

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Author's response to reviews: see over
Dear Editor,

enclosed please find the manuscript entitled “Intergenerational and intrafamilial phenotypic variability in 22q11.2 subjects”, revised as suggested, that we hope is now suitable for publication in BMC Medical Genetics. We did our best to answer to all the questions raised by the Reviewer.

All the authors have read and approved the submission to BMC Medical Genetics.

Enclosed please also find the Response to Reviewers comments, that we found very helpful in further improving the study, and the version of revised paper with clear highlights of all changes made (bold version).

Looking forward to hearing from you,

Sincerely yours,
Claudio Pignata, M.D.

Point by point reply

Major compulsory revisions

1. As observed by the Reviewer, the worsening of the phenotype over generations has already been reported by other Authors (Mc-Donal-McGinn et al 2001, Digilio et Al 2003). In addition, Digilio also hypothesized a molecular mechanism, which could explain the phenomenon of the “genetic anticipation”. Thus, at page 11, line 12 the sentence “and the extension of an unstable mutation at the 22q11.2 locus” has been added.

We accept the Reviewer comment and now in the Discussion the sentence “An ascertainment bias could partially explain this finding in that the first diagnosed subject within a family is likely to be the more severely affected. Moreover, our observation may also be explained by a bias related to the low rate of reproductive fitness of adults with a more severe phenotype.” has been added at page 11, line 3. Moreover, in the “Advantages and limitations of the study”
section we have point out this concept and the sentence “Certainly, an … second generation” has been changed in “The observation that within the families, the patients who were first diagnosed had a higher number of core features as compared to their siblings or parents would suggest an ascertainment bias, even though, as a matter of fact, the clinical phenotype of the parents was milder phenotype than their children.”

2. We share the Reviewer criticism and now the sentence. See answer to point 1 of this reply, on page 11.

As for the data on the siblings of the probands, we agree with the Reviewer interpretation and the sentence “…, a milder phenotype was similarly observed in parents than in the second generation subjects, even though the 5 subjects of the second generation, who were first diagnosed, had a higher number of the major clinical features, as compared to their 6 siblings (16 core features vs 11).” has now been added on Page 9, lines 24. Moreover, in the Advantages and limitations section the sentence “The observation …” has been added and already mentioned in the point 1 of the reply.

3-4. We checked carefully the phenotypes of both participants, in that both 22q11.2DS parents and children have been subjected to the same evaluation protocol, and we are sorry not having considered in its importance the age of the parents, which was missing in the Case Report Form. Now, the age of all the parents and their children has been added. In most cases, the physician who filled the CRF, omitted the age at the diagnosis since it was the same of that of the data collection. Mean age and standard deviation has been recalculated accordingly. The Authors confirm that there are not additional missing data in the study.

**Minor essential revision**

1. On page 8, the term “son” has been changed in child, and on page 11 the term has been removed.
2. In order to improve the clarity of the manuscript we now used the term “second generation”, when possible.

3. We agree with the Reviewer and now the legend to Figure 1 includes the same information as Table 2.

**Discretionary revisions**

1. The term “disorders” has been changed with “features” when appropriate.

2. Grammatical mistakes have been corrected.