Author's response to reviews

Title: Terminal chromosome 4q deletion syndrome in an infant with hearing impairment and moderate syndromic features: review of literature

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Author's response to reviews:

Dear Professor Neri, dear Drs. Ferrero and Zollino,

We wish to thank you for your efforts and informative suggestions that were helpful to the revision process. Your comments have been addressed as follows:

Editor’s comments:
- This is an interesting case report, thoroughly analyzed both clinically and molecularly. However, I think it is too long for a single case report, especially the section dealing with phenotype-genotype correlations.

RESPONSE: The text has been shortened by 342 words (11%). We have toned down our statements on genotype-phenotype correlations and changed the title accordingly.

- Phenotype-genotype correlations is a tricky business and experience tells us that once a correlation seems to be firmly established, a new report will appear, contradicting previous conclusions. There are reasons for this, as explained by one of the reviewers. Therefore I recommend to the authors to be much more synthetic and less "dogmatic" (I apologize for this term, in want of a better one) in affirming phenotype-genotype correlations.

RESPONSE: We have tried very carefully to establish genotype-phenotype correlations with other published and DECIPHER cases with 4q terminal deletion syndrome and, despite all the problems, we believe such reviews are revealing and helpful for clinical syndromologists. We certainly understand that contradictions in the literature exist. In syndromes with a high degree of phenotypic variability, it may be impossible to obtain truly definitive evidence implicating a specific gene in the context of a large structural aberration to a specific phenotype for any given patient. However, such correlations do add some value to the picture. We ensured that the wording is conservative and
acknowledge the limitations of our genotype-phenotype correlations.

-Moreover, there is no need to mention possible imprinting mechanisms, given that the case does not offer evidence to support this contention.
RESPONSE: We have removed the short paragraph discussing the possible role of imprinting genes in the phenotypic variability of this syndrome.

-Likewise, it is not necessary to explain, at the end of the discussion, the mechanisms leading to small genomic imbalances.
RESPONSE: This paragraph was shortened to only include the critical information so that the recombination hotspot figure (Figure 2, bottom) can still be referenced.

-Minor points: the possibility of germinal mosaicism in the mother should be mentioned (it is important to predict the recurrence risk)
RESPONSE: This was added to the discussion (page 12, middle).

-On p. 10 the expression "between the beginning of the case we present and the end of case #20" sounds more colloquial than scientifically terse
RESPONSE: This sentence was re-phrased: “The second CHD locus (chr. 4: 184,046,156-186,997,806 bp) maps in a region containing 12 out of 17 overlapping cases with cardiac phenotypes (Figure 2, red), two of whom uniquely overlap with this region.”

-On p. 12, I am not sure what the authors mean by "phenotypic disunity". This expression is new to me.
RESPONSE: This was modified as “phenotypic variability.” The initial usage was intended to convey the “spectrum” of phenotypes ranging from completely normal to a wide range of syndromic features of variable severity that cannot be easily inferred by the presence of the deletion alone.

-Editorial requirements: Please include the email address of all authors in the title page.
RESPONSE: Email addresses of all authors were added to the title page according to the journal style.

Reviewer 1:
Reviewer’s report
Title: Terminal chromosome 4q deletion syndrome: a case report and mapping of critical intervals for associated phenotypes
Version: 1
Date: 7 May 2014
Reviewer: giovanni battista ferrero
Reviewer’s report:
This is an interesting paper describing a rare case of terminal chromosome 4q
deletion. The authors propose several critical intervals for specific features of the syndrome based on a detailed analysis of the data available in the literature and in DECIPHER database.

The role of several specific genes is discussed providing new candidate genes involved in the pathogenesis of CP, CHD, ASD.

Level of interest: An article whose findings are important to those with closely related research interests

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

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I have no competing interests to declare

RESPONSE: The quality of English was reviewed.

Reviewer 2:
Reviewer's report
Title: Terminal chromosome 4q deletion syndrome: a case report and mapping of critical intervals for associated phenotypes
Version: 1
Date: 20 May 2014
Reviewer: Marcella Zollino
Reviewer's report:
Vona et al report on a case of terminal chromosome 4q deletion syndrome, which is discussed along with several additional cases reported in DECIPHER, in the attempt of mapping critical intervals for associated phenotypes. This is a single case report, in which a relatively large 4q35.1q35.2 deletion is associated to subtle phenotypic features, namely CHD, hearing impairment, cryptorchidism and sub-mucous cleft palate. Of note, normal intellectual development was described. Authors made a great effort in dissecting the nonspecific and highly variable phenotypes associated with partial 4q deletions, and in discussing about candidate genes for some key features. Genetic test are appropriated.

However several criticisms are in order:
- Large chromosome deletions, as the present one, make the pathogenic link between haploinsufficiency of specific genes and distinctive clinical signs questionable (positional effect?, complex model of pathogenesis?)
RESPONSE: Since the importance of haploinsufficiency is clouded by other possible pathogenic mechanisms, references to haploinsufficiency were toned down. The corresponding haploinsufficiency column in Table S1 was removed.

- DECIPHER data, although helpful, are incomplete in some cases, as considered by the authors
RESPONSE: The limitation of the DECIPHER cases was disclosed. We nonetheless find them helpful, since there were a limited number of publications
discussing patients with deletions unique to this region. Additionally, we found
the array information provided in the DECIPHER database was extremely helpful
allowing a comprehensive comparison of deletion intervals in a significant
number of unrelated patients to assemble Figure 2 showing potential
genotype-phenotype correlation. Furthermore, the combination of literature and
DECIPHER reports has not been described before, which could be interesting for
readers.

- The present genotype-phenotype correlation analysis further confirms that
several features characterizing the 4q deletion syndrome phenotype show
significant incomplete penetrance; in addition, other signs (see cryptorchidism)
are nonspecific.

RESPONSE: It is true that the genotype-phenotype analysis presented in this
manuscript is not a holistic description of the syndrome; however, given the
seemingly broad phenotypic presentation possible (in part due to the possibility
of incomplete penetrance), some degree of phenotypic delineation could be
helpful for clinicians with patients having deletions similar to the ones presented
here. Three out of twelve male patients had cryptorchidism (Table S2), which,
although may seem non-specific, could be of more significance in eventual
publications describing more male patients.

- The final message of the MS cannot be easily inferred.
RESPONSE: Although our aim was to reduce the amount of text (by >10%), we
included a final concluding section at the end of the discussion to highlight the
final message of the MS.

Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: No competing interests