Author's response to reviews

**Title:** Cryptic FMR1 mosaic deletion in a phenotypically normal mother of a boy with Fragile X Syndrome: case report

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**Author's response to reviews:** see over
Dear Editors,

Many thanks for handling our manuscript. We appreciate the reviewer’s suggestions and the following is our revision with respect to the comments. The revised manuscript has been formatted according to the journal style. The original Figure 3 legend (334 words) has been shortened (less than 300 words). A misplaced grant number has also been corrected.

Reviewer: Giovanni Neri
Reviewer's report:
Minor essential revisions

On p. 9 and again in the Conclusions section the expression "focused prenatal diagnosis is strongly recommended for normal conception" should be changed to "focused prenatal diagnosis is strongly recommended to verify the normality of the fetus".

Answer:
1) The expression has been changed on p. 9 and in the Conclusions section.

p. 9 Original: "focused prenatal diagnosis is strongly recommended for normal conception"

p. 9 Corrected: "prenatal diagnosis is recommended to exclude recurrence"

Conclusions section Original: "obligatory prenatal tests are required for normal conception"

Conclusions section Corrected: "obligatory prenatal tests are required to verify the normality of the fetus"

The authors should not overemphasize the need to do the kind of careful study they did, just for the sake of prenatal diagnosis. In a case like this, even if the mother had been found normal in all tissues, prenatal diagnosis would still be indicated, given the possibility of a germline-confined mosaicism.

Answer:
2) We agree with the reviewer’s opinion, and amendments have been made to modify the tune of the sentences in our manuscript. Some repetitive sentences are also removed.

E.g. on page 4:

Original: "focused prenatal diagnosis is strongly recommended for normal conception"

Corrected: "prenatal diagnosis is recommended to exclude recurrence"

On page 10:

Original: "extensive examinations of multiple tissue samples are highly recommended for estimation of the status in germ cells"

Corrected: "extensive examinations of multiple tissue samples are highly recommended"

Since the presence of mosaicism results in an increased transmission risk, breakpoints mapping and examination of different tissues may help individualized prenatal diagnosis.
In Fig. 2C there is a symbol for the proband, which however is not visible in the bar graph.

Answer:

3) Fig. 2C shows the qPCR results with three sets of primers within the region that is deleted in the proband. The symbol for the proband is not visible in the bar graph because no products were obtained.

Reviewer: Pietro Chiurazzi

Reviewer's report:

This case report illustrates well the need for thorough investigation of several tissues in order to find evidence for possible mosaicism of apparently de novo mutations. The Authors report on a mother who had her first son with an apparently de novo deletion of the FMR1 gene and a fragile X syndrome phenotype. They succeeded in the identification of tissue mosaicism in skin and eyebrow fibroblasts.

I have made a number of minor changes that I suggest to accept and they are indicated in red in the attached PDF copy of the proofs.

Answer:

We value all the amendments proposed by the reviewer. By addressing them, our manuscript becomes more concise and to the point. The changes as indicated in red in the attached PDF file have been accepted.

On page 7, reviewer proposed a question that "Are these different from F1 and R1 because they correspond to a smaller amplicon?" And yes, the primer pair F2 and R2 differs from F1 and R1 because they correspond to a smaller amplicon (159bp). We first mapped the breakpoints of amplified product with primers F1 and R1. Given that amplicon less than 200bp is most suitable for quantitative PCR, another primer pair (F2 and R2) was designed based on the reference sequence around the breakpoints.

Thank you very much for your attention and consideration. If any parts of the manuscript need further improvement, please inform us for revision. I'm looking forward to hearing from you soon.

With kind regards,
Sincerely,
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