Author's response to reviews

Title: Autism Spectrum Disorder in Microphthalmia with Linear Skin Defects Syndrome

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

We really thank the reviewer for the useful comments and suggestions that improved our paper titled “Microphthalmia with Linear Skin Defects (MLS) associated with Autism Spectrum Disorder (ASD) in a patient with Familial 12.9 Mb Terminal Xp deletion”

We answered all the queries point by point.

Reviewer

Major Points:

1. The coexistence of MLS with ASD in this patient does not prove causality. Therefore, the title as well as parts of the discussion are misleading since they imply causal relationship.

   *As suggested, we have modified the title in “Microphthalmia with Linear Skin Defects (MLS) associated with Autism Spectrum Disorder (ASD) in a patient with Familial 12.9 Mb Terminal Xp deletion”*

2. The emphasis of this manuscript should be on the Xp22.32-p22.2 deletion and the associated contiguous gene syndrome. To this end, the authors should better define the breakpoints of the deletion and compare it to previously reported cases. Which platform was used for aCGH? How the deletion was detected in the mother (FISH or aCGH)?

   *The breakpoints have been detailed, and a comparison with other cases has been added in the Conclusion (pages 8-9). The platform, and the genetic investigations performed in the mother have been inserted (section Genetic investigation)*

3. The authors rightly indicated that the ASD in this patient is most likely related to autism related genes but unfortunately they did not elaborate on these genes.

   *In the Conclusion section we have added specific comments on autism related genes.*

4. The authors briefly discuss potential mechanisms for phenotypic variability including skewed X-inactivation and somatic mosaicism. I am wondering if these mechanisms were studied in the proband and her mother.

   *The X-inactivation studies were not described because not relevant to clear mother/daughter phenotypic differences (similarly to other cases published in literature). However the results have been inserted (section Genetic investigation), and the mechanisms of X-inactivation and somatic mosaicism extensively discussed in the Conclusion section.*

5. The mother was found to have the same deletion but a detailed phenotypic characterization of the mother was not provided.

   *Specific data have been added in the Case presentation.*
6. The first paragraph of Discussion is not needed. This information can be found in any textbook.

As suggested, we have simplified the first paragraph of Conclusion section

Minor Points:

1. The official name of HCCS is holocytochrome c-type synthase

As suggested, we have modified the official name of HCCS

2. Please use intellectual disability instead of mental retardation (MR)

The term mental retardation was substituted with intellectual disability

3. Reword “Noting that cytochrome c is the final product of HCCS activity,…”

We have reformulated the sentence

4. Provide details on anxiety disorders and epilepsy in the family history.

we added that epilepsy and anxiety history was found in the mother’s family

5. IUGR is difficult to diagnose before 18-20 weeks of gestation. I am wondering how the diagnosis was made during 1st trimester in this patient.

Thank for this revision. The intrauterine growth restriction was revealed in the third trimester of pregnancy.

6. Reword: “resulted negative at genetic analyse.”

As suggested, we have modified this sentence

7. Is the micromelia part of the Xp22.32-p22.2 deletion?

Yes, being deleted the SHOX gene. A specific comment has been added in the Conclusion.

8. Did brain MRI show brain atrophy and or microcephaly, which observed by PE?

The MRI did not show neither brain atrophy nor microcephaly, therefore this data has not been discussed

To Editor

We modified the contributions of author Francesco Craig
-Since an extensive revision about genetic data was performed, we require to move the Prof. Gentile from Acknowledgements to Authors

We will be indebted with the Editorial board if this revised paper can now be considered for the possible publication in the Journal.

Many thanks in advance for your courtesy
Lucia Margari