Author’s response to reviews

Title: A new case of de novo 6q24.2-q25.2 deletion on paternal chromosome 6 with a Silver-Russell-like phenotype and growth hormone deficiency: a twelve-year follow-up and literature review

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

we would like to re-submit the article MS: 2140119309133667 “A new case of de novo 6q24.2-q25.2 Deletion on Paternal Chromosome 6 with Silver-Russell-like Phenotype and GH Deficiency: twelve years follow-up and literature review”, revised and modified according to the reviewers’ suggestions.

First of all, we would like to thank the reviewers for the kind appreciation of the manuscript and also for their helpful comments and criticisms. We revised and modified the manuscript, according to these suggestions and we hope that we did it properly.

We have created this point-by-point list of corrections according to the reviewers’ comments.

EDITOR’S COMMENTS:

FORMATTING REQUIREMENTS:

1) Please include the email address of all authors in the title page.
We have added the email address of all authors in the title page as for Editor request.

2) Ethics statement: Research involving human subjects (including human material or human data) that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html). A statement to this effect must appear in the Case Presentation section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.
We have added a Consent form in the text (page 10 lines 12-15). This study was approved by the our Ethics Committee. Parents of the patient have given their consent for the Case reports to be published.

3)Please confirm that the patient has given their consent for the case report to be published and please include a Consent section in the manuscript stating that consent has been obtained. The editorial office may request copies of the informed consent documentation at any time. We recommend the following wording is used for the consent section: "Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal."

We have added a Consent form in the text (page 10 lines 12-15). This study was approved by the our Ethics Committee. Parents of the patient have given their consent for the Case reports to be published.

4)Acknowledgements: We strongly encourage you to include an Acknowledgements section between the Authors? contributions section and Reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study.

We have added a Acknowledgements section in the text (page 11 lines 15-16).
Reviewer 1 report

Pawel Stankiewicz

Reviewer’s report: In the manuscript “A new case of de novo 6q24.3 Deletion on Paternal Chromosome 6 with Growth Hormone Deficiency: a twelve years follow-up”, Stagi et al. describe an apparently de novo 11 Mb deletion on paternal chromosome 6q24.2q25.2 identified in a 6-year-old boy with IUGR, postnatal growth failure with growth hormone deficiency, mild developmental delay, delayed bone age, hypophyseal hypoplasia, bilateral pseudopapilledema, hyperopic astigmatism, dysmorphic features, hypoplastic left colon, heart defects, GERD, and bilateral inguinal hernia. The Authors correlate the patient’s phenotype with the maternally imprinted PLAGL1 (ZAC1) gene on 6q24.2 and review the literature. They also propose to name this deletion “Nowaczyk syndrome”. The manuscript adds to the literature. The data sound and well controlled.

First of all, we would like to thank the reviewer for the kind appreciation of the manuscript and also for the helpful comments and criticisms. We revised and modified the manuscript, according to these suggestions and we hope that we did it properly.

Major Compulsory Revisions

The Authors should also discuss the overlapping deletions from Decipher. Was the paternal sample analyzed to exclude a balanced insertional translocation? Title 6q24.3 should be changed to 6q24.2-q25.2
We thank the Reviewer for the suggestion. We have changed the title as for Reviewer suggestion. However we have added a “genetic analysis section” in the text (pages 7-8). We have evaluated the paternal sample and we have added this aspect in the text. However, we have discuss the overlapping deletion from decipher in the text.

Abstract

Deletions on the long arm of chromosome 6 are relatively uncommon, and only a small number occur on the paternal copy, causing growth deficit. This sentence can be misleading. The Authors refer only to the distal portion of 6q. We thank the Reviewer for the suggestion. We have changed this phrases as for Reviewer suggestion and we hope that it is now not misleading.

Birth weight was 1740 gr (-1.6 SDS), the length was 43.5 cm (-1.1 SDS), and the head circumference was 32.2 cm (0.0 SDS). At the age of 3.75 years, his height was 88.2 cm (-2.98 SDS), weight 11.500 kg (-3.34 SDS), and his body mass index was 14.78 (-0.81 SDS). Please delete these sentences from Abstract. We thank the Reviewer for this suggestion. We have deleted these informations as for the Reviewers suggestions.

Figure 1 The facial phenotype is not well shown with the bars over the eyes, so the similarities with the reported cases cannot be well judged.
We thank for the Reviewer suggestion. We have sent new photos with reduced bars over the eyes. We hope that the phenotypes may be better evaluated.

Minor Essential Revisions
Mental retardation should read intellectual disability.
We are sorry for the mistake. We have corrected these terms as for Reviewer suggestion.

Case presentation “Prenatal ultrasounds ... paternal disomy.” Please move this para before “His birth was...”
We thanks the Reviewer for the suggestion. We have rephrased the text as for reviewer suggestion.

Was cardiomegaly followed postnatally?
The cardiomegaly was not confirmed postnatally. We have added this information in the text (page 5 line 12).

Satellite analysis of chromosomes 2, 11, and 16 showed biparental inheritance, The Authors probably mean microsatellite analysis.
We are sorry for the mistake. We have corrected the term as for Reviewer suggestion.

At 2 years of age, he underwent a left inguinal herniotomy. What about the right hernia?
We are sorry for the mistake. We have corrected the text. The herniotmy was bilateral (page 6, lines 2-3).
Figure 2 is poorly explained in its legend. I suggest showing a schematic representation of this chromosomal region with other reported overlapping deletions depicted. Also, please provide the deletion coordinates in the text or figure legend. It is unclear whether PLAGL1 is deleted in the patient.

We are sorry for this aspect. We have added in the text a specific Genetic analysis section. we have renamed Figure 2 (now Figure 3) and we have added in the figure 3 also the array CGH analysis with high resolution (figure 3b).

Figure 3 should be moved to Supplement.

We thank the Reviewer for the suggestion. We have moved the figure 3 (now Figure 4) in the supplement.

Discretionary revisions

Abstract

Kumar and Nowaczyk should read Kumar et al. [13] and Nowaczyk et al. [14]

We thank the Rewiever for the suggestion. We have corrected the text as for reviewer suggestion.

Case presentation 1740 gr Change to 1740 g

We thank the Rewiever for the suggestion. We have corrected the text as for reviewer suggestion.

cornelis noordam
Reviewer's report: The authors report a further case report on this relatively rare condition. It contributes on the knowledge of growth in this condition and the possible benefit of hGH treatment. Major comments 1.

First of all, we would like to thank the reviewer for the kind appreciation of the manuscript and also for the helpful comments and criticisms. We revised and modified the manuscript, according to these suggestions and we hope that we did it properly.

Page 3 IUGR: please reformulate into SGA 2.

We are sorry for the mistake. We have corrected the abstract as for Reviewer suggestion. So we have rephrased the text.

Page 4 paragraph 5: Details on development can be reported upon more global e.g. development was only slightly delayed 3.

We thank the Reviewer for the suggestion. We have abbreviated the text as for suggestions.

Page 5: The clinical description and the longitudinal description should be abbreviated; it is far too long 4.

We thank the Reviewer for the suggestion. We have abbreviated the text as for suggestions.

Page 5 paragraph 2 and 3: Please provide normal values for IGF1 and IGFBP3; these values do not appear as too low to me 5.

We thank the Reviewer for the suggestion. We have added the reference range for IGF-1 and IGFBP-3 and we have rephrased the text as for Reviewer suggestion.
page 6 last paragraph details on growth are also reported in the growth curve and are not helpful.

6.

We thank the Reviewer for the suggestion. We have abbreviated the text as for suggestions.

page 7, 8 and 9 can be written more concise; eg the same conclusion on the use of hGH is written twice; I would say that this part could be reduced to 60 % of the current length.

We thank the Reviewer for the suggestion. We have abbreviated the text as for suggestions.