Author’s response to reviews

Title: Childhood neurodegeneration associated with a specific UBTF variant: a new case report and review of the literature

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Author’s response to reviews:

Dear editorial board,

Please find attached the reviewed version of the manuscript “Childhood neurodegeneration associated with a specific UBTF variant: a new case report and review of the literature”. We read the comments carefully and you will find our answers below. We thank the reviewers for their relevant and constructive suggestions that helped to improve the manuscript.
1. REVIEWER 1 (Simon Edvardson)

Comments to the author: “I thank the editor for being invited to review this paper. The Authors have identified a child with a known disease-causing UBTF-variant and add information regarding a peculiar EEG-pattern in their patient. This may be a useful phenotypic marker if identified in further patients. My main concern is that this EEG-abnormality may be unrelated to the UBTF-variant. It would thus be useful to include other De Novo or Biallelic variants found in this child that could have bearing on this concern. I find the table included useful as a summary of the clinical features of patients hitherto described.”

We fully agree with this recommendation. To address it we have added further information on the genetic analysis results in the Case presentation section, included a new reference in this same section (reference 7: Symonds et al 2019) and discussed this point further in the Discussion and Conclusions section as follows:

- Case presentation, lines 97 to 105:

“The raw data from Whole Exome Sequencing (WES) were screened using an in-house pipeline as previously described (6) allowing for filtering of synonymous and common variants to which a panel of approximately 1300 genes known to be implicated in developmental delay and seizure disorders was applied. The original analysis failed to yield any variant that might be plausibly linked to an intellectual disability or epilepsy phenotype (7). The data were reanalyzed six months later using an updated panel that (at that point) contained the gene UBTF, that had just been published in connection with an intellectual disability phenotype by Edvardson et al (1). This allowed for the detection of a heterozygous c.628G>A UBTF variant, which was confirmed by Sanger sequencing and found to be de novo.”

- Discussion and Conclusions, lines 157 to 160:

“Data analysis failed to reveal other variants that might have plausibly accounted for the EEG abnormality, either under a recessive or a de novo dominant model (7). Therefore, we suggest that this may be part of the clinical syndrome associated with the c.628 C>G UBTF variant and we wonder whether it relates to a particular stage of the disease.”

1. REVIEWER 2 (Pierro Pavone)

ADDITIONAL REQUESTS/SUGGESTIONS: Figures #1 could benefit from better labeling.

We fully agree with this suggestion and we have added a legend to Figure #1, that can be found in the Figures section at the end of the manuscript, as follows:
Figure 1, Legend, lines 223 to 226:

“Diagram illustrating time course of disease in our patient. Dotted grey line: normal developmental trajectory; Red Line: developmental trajectory in our patient; Blue boxes: main signs and symptoms; Orange box: highlights period of subacute deterioration possibly triggered by infection.”

We hope the changes we have made addressed fully the concerns of the reviewers and editorial board and that this reviewed version of the manuscript be found suitable for publication.

We are looking forward to hearing of your dispositions.

Yours sincerely,

Filipa Bastos

on behalf of the authors