Title: A syndrome of lethal familial hyperekplexia associated with brain malformation.

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

Many thanks for peer reviewing the above-mentioned manuscript. We would first like to thank the reviewers for their valuable efforts, enlightening ideas and for the pertinent comments. The manuscript has been revised accordingly, and extensive modifications were made. The revised version will be uploaded with the changes (in red). We have also specified in the Methods Section that we had consent to publish the images and videos.

The following (in red) are clarifications to the points raised by the Referees.

Referee 1


We have incorporated this in the manuscript together with the references.
The authors should also comment on the nature and types of GlyT2 mutations, which are associated with severe neonatal apnea episodes (Rees et al 2006, Nat Genet 38:801-806) in the introduction on page 4.

Comments on the nature and types of GlyT2 mutations were added to the manuscript, as well as the reference.

2. Further methodological details and data should be provided on the homozygosity scans conducted by the authors. At present there is no data in the paper that supports the author’s assertion that ‘none of the known hyperekplexia genes were present within the overlapping regions of homozygosity’ (pages 2 and 7). Since the authors appear to have exclusive access to this kindred and associated DNA samples, there is no obvious reason for withholding this data. Information should be provided on: i) the number of regions of homozygosity found; ii) chromosomal locations and co-ordinates; iii) potential candidate genes.

We appreciate the Referees comments, but since the exome sequencing is underway to identify the disease causing mutation in this family, we opted to defer the data on the homozygosity scan to include it in a future genetic paper describing what we anticipate to be a novel gene. We have added the statement (data not shown) in Page 11 to clarify that.

3. On page 8 of the discussion, the authors state that the prognosis of HPX is usually favourable with spontaneous amelioration of hypertonia’. The authors should be careful here to ensure that they refer to human hyperekplexia/startle disease. GlyT2 mutations result in early neonatal lethality in mice, cows and dogs – see Gill et al 2011, Neurobiol Dis 43:184-189; Charlier et al 2008, Nat Genet 40:449-454.

We have incorporated this in the manuscript together with the references.

4. Given that the authors suggest that this is an autosomal recessive disorder, I am surprised by the number of affected individuals in the kindred shown in figure 1. The number of affected individuals is clearly far higher than the ratio predicted by classical mendelian genetics. The authors should comment on this.

Comments on this were added to the manuscript, as well as a new reference [32].
Minor Essential Revisions:
Some labelling of key structures refereed to in the figure 2 legend on panels A-H would be useful for the reader.

A modified Figure 2, with labeling, will be uploaded.

Discretionary Revisions:
Although the authors have not yet presented their homozygosity mapping data, in tandem with exome sequencing, it should be possible to identify the causal mutation for this disorder. I therefore wonder whether the publication of this clinical data, although interesting, is premature until more is known about the causative gene.

We think that publishing the clinical phenotype of a novel syndrome is important; not just because it defines a new syndrome but also for allowing us to be contacted by others who may have patients with a similar phenotype which will help us identify, in the future, additional mutations in that gene.

Referee 2

1. First Problem: Structure. At present, it's a lump of long paragraphs and is hard to follow. I'd recommend using sections and subsections: Patient 1. Patient 2, also abstract, introduction, case report and discussion. And please consider separate paragraphs for initial clinical presentation, workup, subsequent clinical events and MRI findings for each patient.

The manuscript was extensively re-structured to adopt the Reviewer's suggestions.

Discussion:
CNS findings, MRI Findings, Neurophysiological Findings, EEG findings. Conclude with a few paragraphs about how your patients do or do not fit "classic" lethal familial hyperekplexia syndrome. Finally a paragraph about the literature review.

The manuscript was extensively re-structured to adopt the Reviewer's suggestions.
2. Second Problem: Content. This manuscript purports to focus on brain malformations but does not provide enough detail. More information about the epilepsy would have been most useful (what did the EEGs show? What types of seizures did the pts have? How well did the medications work?). Supportive information about the degree of motor + cognitive impairment would also have been helpful. The biggest problem is with the discussion of radiographic findings. The authors lump together what has been described radiographically with what has been found pathologically. I propose clearly description of MRI finding in small but understanding paragraph, also the same on figure legends.

The manuscript was extensively re-structured to adopt the Reviewer’s suggestions in these aspects. The legend for the imaging figure (Figure 2) was modified and clarified. A new Figure 2 was uploaded.

3. Third problem: figures and genealogy. Please make them more understanding, especially the figure legends and mark them correctly in the paper.

A key explaining the genealogy was added to a new modified Figure 1, which will be uploaded.

We hope that we have clarified all points and that the new version of the paper will be up to the expectations of your readership.

Best wishes and regards

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