Reviewer's report

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

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Reviewer: Robert Harvey

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Review of BMC Neurology manuscript: 'A syndrome of lethal familial hyperekplexia associated with brain malformation' by Seidahmed et al

This is an interesting report, describing a new syndrome in a Saudi Arabian kindred associated with hyperekplexia, excessive foetal movements, microcephaly and defects in cerebellar development. These defects lead to the premature death of six affected individuals, underlining the importance of determining the genetic cause of this new autosomal recessive disorder.

Major Compulsory Revisions:

1. The introduction to the manuscript is informative and largely accurate. However, it should be noted that mutations in ARHGEF9, encoding collybistin and GPHN, encoding gephyrin are not thought to be commonly associated with hyperekplexia. Rather, mutations in ARHGEF9 are associated with X-linked intellectual disability (Shimojima et al 2011, J Hum Genet 56:561-565; Lesca et al 2011, Am J Med Genet A 155A:1706-1711; Marco et al 2009, BMJ Case Rep pii: bcr06.2009.1999; Kalscheuer et al 2009, Hum Mutat 30:61-68) whilst mutations in GPNH are associated with molybdenum co-factor deficiency (Reiss et al 2011, Clin Genet 80:598-599; Reiss et al 2001, Am J Hum Genet 68:208-213). 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.

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.

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.

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.

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.

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.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests