Reviewer's report

Title: Novel SPAST deletion and reduced DPY30 expression in a Spastic Paraplegia type 4 kindred

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Reviewer: Conceicao Bettencourt

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Comments to the authors

Racis and colleagues present a case report on an interesting AD-HSP family harbouring a novel SPAST deletion, which affects not only SPAST but also DPY30 expression levels. However, there are several issues that should be addressed to improve the manuscript.

Major Compulsory Revisions:

- In the Case presentation (page 4, last sentence) the authors say that the deceased father and two uncles of the index case showed similar gait disturbances. However, the information about affected and unaffected members, which is important, is not shown in the family pedigree (Fig. 1).

- The nomenclature of the novel mutation should be carefully revised according to HGVS recommendations (http://www.hgvs.org/mutnomen/). For example, the break point is closer to the end of intron 4 than to the beginning of this intron and it should be numbered accordingly. Furthermore, the reference sequence used for nucleotide numbering should be indicated.

- Also, it should be noticed that this novel deletion affects not only the 5' UTR of SPAST gene but also further upstream sequences, which likely include additional regulatory elements not only for SPAST but also for DPY30. This information should be included and discussed.

- The fact that there is an asymptomatic carrier of the novel mutation should be further discussed. The authors’ state (page 6): “... not penetrant IV-25...” Could it be the case that this individual is still too young with respect to the mean age at onset for this family?

- The authors’ also state (page 6): “The mean (SD) disease duration was 13.2 (13.4) years (range 6-35), and it correlated well with clinical severity.” How was this correlation measured?

- In the Discussion, the authors say that the Japanese family described by Iwanaga et al. (2005) shows clinical features and disease duration highly similar to their family. A second Japanese family, described by Miura et al. (2011), harboring a deletion that spans from part of SPAST to part of DPY30, shows a much earlier mean age at onset, exhibits additional clinical features and all female patients have had miscarriages. Given the fact that the novel deletion, reported by Racis and colleagues, spans further upstream the SPAST gene,
affecting also the expression of DPY30, shouldn’t one expect a greater similarity with the second Japanese family described by Miura et al. (2011)? The authors should discuss this further.

Minor Essential Revisions:
- Concerning the Background, there is a very recent paper reporting novel HSP loci and genes, surpassing now 70 HSP loci (Novarino et al., Science. 2014 Jan 31;343(6170):506-11), which would be worthy to reference.
- Instead of “punctuate mutations” the authors should say “point mutations” (page 6, line 1).
- Figure 3 includes an extra grey square in the legend that should be removed.
- The English needs revisions of minor grammatical errors.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**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.