Reviewer's report

Title: Mutational spectrum of the SPG4 (SPAST) and SPG3A (ATL1) genes in Spanish patients with hereditary spastic paraplegia

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Reviewer: Kirsten Svenstrup

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The authors report data from a large (370 patients) cohort of HSP patients. DNA from these patients have been sequenced in the SPAST gene, and the remaining patients with age of onset below 20 years also in ATL1. Where mutations were not found MLPA was performed. Splice mutations were confirmed by RT-PCR analysis. For new mutations segregation analysis was performed and 400 controls were used. The authors report several new mutations and polymorphisms and in combination with the segregation analysis these data are important to publish in order to improve genetic counselling for HP patients.

Major Compulsory Revisions

1) The manuscript should be significantly reduced in length (to at least 50%). The language could generally be more precise.

2) The references should be more precise. It is not clear which criteria references are chosen from when many references are cited. Example: To date >150 SPAST mutations have been reported (http://www.hgmd.cf.ac.uk/hgmd0.html), mainly in patients with pure HSP although other associated neurological symptoms/findings (cognitive impairment, mental retardation, cerebellar ataxia, neuropathy) have been found in some families[7-12].

Several referenced are not cited correctly. Examples: The disease is classified as "pure" when spasticity is the only clinical finding, and as "complicated" when other clinical features such as seizures, dementia, cerebellar ataxia, epilepsy, or peripheral neuropathy, are also present [1]. And: This suggested that both, haploinsufficiency and "toxic" gain of function could explain the pathogenic mechanism of SPAST mutations [17-19]. Ref 24 and 25 do not support "SPG3A is usually found in early onset cases (childhood or adolescence)" since only early onset cases are included in these studies.

3) The analysis of SIFT scores should be excluded. The power of the reported study is that conclusions of pathogenicity of mutations can be drawn from the presented data and not from an algorithm. Pedigrees of all new mutations should be presented in a figure.

Minor Essential Revisions:

1) Human gene names should be in italics.
2) The DNA variants are stated to follow guidelines from HGVC but they use one letter amino acid code

3) Figures should include both family identification and mutation on cDNA and protein level

4) On which criterias was AD suspected and how were siblings with healthy parents categorized (Patients)

5) Existence of pyramidal signs and examination by a qualified neurologist do not fullfill the criterias for HSP (patients)

6) What is the difference between neuropathy and periferal neuropathy? (Patient characteristics)

7) I do not understand the sentence: Our work showed a heterogeneous behaviour for these mutations and this would make difficult to establish a genotype-phenotype correlation. (Conclusion)

8) In fig 2: What does P M Cand G mean?

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

**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'