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: Filippo M. Santorelli

Reviewer’s report:

This manuscript presents the mutational spectrum of two frequent etiologies in hereditary spastic paraplegia (HSP), namely the SPAST and ATL1 genes, in a large cohort of Spanish patients.

The settings of this paper are the following:

Study design: multicenter, genetic analyses
Target disease: hereditary spastic paraplegia (either dominant or apparently sporadic)
Endpoint: ascertain relative mutation frequency in Spain

The manuscript shows that about 15% of 370 patients with spastic paraplegia harbor a mutation in SPAST/SPG4 or ATL1/SPG3A.

The design of the study seems appropriate and methodologies are sound. The novelty is limited in that it reports a large number of new mutations without their full functional characterization. Also, clinical data are scanty and genotype/phenotype correlations could have been improved if the Authors had considered assessment of disease severity (e.g., SPRS scores, Schule et al. Neurology 2006) or functional evaluation of quality of life (e.g., Barthel index). However, it is important to know regional relative frequencies of known molecular etiologies for “rare” neurological disorders.

In my opinion the manuscript is of merit but can be improved, as follow:

Abstract:
- It should be stated how many index cases were examined in a total of 370, and how many were presenting with a pure phenotype.
- It should be stated how many familial cases harbored mutations in one of the two genes and how many sporadic/unclear transmission patients proved to be positive upon full gene testing.

Introduction
- Gene names should be italicized.
- For the sake of clarity, indicate at first mention the spastin and atlastin genes as SPAST/SPG4 and ATL1/SPG3A, respectively.
- Add latest date of consultation of the gene specific database.
- References should be presented consistently following the journal guidelines (no superscript references, please)

Patients & Methods
- Considering the number of patients, state unequivocally index cases only. Divide them in familial (and n of families) (that is, those with a positive family history) and “apparent” sporadic those with parents who were alive and did not present subjective neurological complaints or could not be examined or unsure past medical history.
- MLPA analysis section should precede Analysis of SPAST transcripts
- Avoid the use of not canonical jargon (for example SP).
- It would be important to have comparisons between disease duration, severity and quality of life at least in ADHSP with mutations in SPAST, ATL1 and patients with no mutations.

Results
- See above for index patients and relative frequency of mutations.
- State clearly criteria adopted to assess pathogenicity for variants identified in this study.
- Since the disease-related status seems uncertain, the p.I328L mutation should be removed from the list of pathogenic mutations. Although it could be related to a clinical phenotype with reduced penetrance, the variant has a low predicted deleterious value and it seems not sufficient per se to cause spastic paraplegia. In my opinion, it is safer to list p.I328L among polymorphisms. In supplementary table 2 it could be just added a note to indicate uncertainty.
- Genotype-phenotype correlations could be improved if one considers severity scores and Barthel index.

Discussion
- Re-writing the Results section might help to have a more focused discussion. As an example, it is sufficient to discuss the relative frequency of SPAST and ATL1 mutation in the Authors’ cohort in comparison with published data, indicate the type of mutations identified (including sense mutations), a few words missense variants affecting splicing when they reside in exon-enhancement sequencing for splicing, and a relatively low frequency of multi-exon deletions/duplications.
- Based on the fortunate large number of molecularly-tested patients in this study, readers would appreciate a sort of flowchart for molecular strategies in case of pure or complex phenotypes, familial or apparently sporadic patients, and early or late-onset disease onset.

Figures and Tables
Quality of Supplem. Figure can be improved. Please, use a different ID code for
patients in Supplementary fig. Commonly, SPGXX is used to indicate HSP loci or genes and it is better not to use in patients to avoid confusion in readers.

**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