Author’s response to reviews

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

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Author’s response to reviews:

Editor-in-Chief
BMC Medical Genetics
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RE: MS: 1434273587118720

Dear Editor,

Enclosed please find the revised version of a manuscript entitled “Novel SPAST deletion and reduced DPY30 expression in a Spastic Paraplegia type 4 kindred” by doctors Racis, colleagues and myself, for possible publication in BMC Medical Genetics. We have modified the text according to your suggestions. A list of the modifications and the responses to reviewers’ concerns are listed point-by-point in the attached document. Changes have been highlighted in the revised manuscript.

Reviewer # 1.

1. 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 clinical state of the proband’s father and two uncles was shown in the family pedigree-Figure 1. Legend to Figure 1 has been modified accordingly, also to account for the points raised by Referee #2.

2. The nomenclature of the novel mutation should be carefully revised according to HGVS recommendations (http://www.hgvs.org/mutnomen/). For example, .... used for nucleotide numbering should be indicated.
The nomenclature of the deletion mutation was modified (see page 6, ln 4).

3. 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.

We modified the text accordingly, as suggested (see page 6, ln 4; page 7, ln 6).

4. 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?

We further discussed this issue in the revised manuscript, recognizing that at this point we cannot sort between case IV-25 developing later in life clinical manifestations or being a case of true non penetrant mutation (see page 6, ln 1-5 from bottom).

5. 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?

Disease duration was correlated with the SPRS score (see Abstract and page 6, ln 16).

6. In the Discussion, the authors say that the Japanese family described by Iwanaga et al. (2005) shows clinical features and ..... Given the fact that the novel deletion, reported by Racis and colleagues... shouldn't one expect a greater similarity with the second Japanese family described by Miura et al. (2011)? The authors should discuss this further.

We discussed further this issue in the revised manuscript (see page 8, ln 1).

Minor revisions:

7. 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.

The work by Novarino and colleagues was cited in the Introduction. The list of references has been updated and numbers modified accordingly.

8. Instead of “punctuate mutations” the authors should say “point mutations” (page 6, line 1).

“Point mutations” replaced “punctuate mutations”. See text page 6, ln 1.

9. Figure 3 includes an extra grey square in the legend that should be removed.

The Figure 3 was corrected, as suggested.
10. The English needs revisions of minor grammatical errors.

Minor grammatical mistakes were corrected and the text was revised and edited by a native English colleague (Dr. C. J. Wrenn). She is thanked in the acknowledgements.

Reviewer #2.

Minor Comments

1. In the Introduction reference should be made to Novarino's et al.'s paper "Exome Sequencing Links Corticospinal Motor Neuron Disease to Common Neurodegenerative Disorders". They identified 18 previously unknown candidates for AR-HSP.

This was taken into account. See note 7 to Reviewer #1.

2. The authors note miscarriage in one of the affected, and bring up the possibility of it's relation to DPY30. It would be a good idea to add the number of gravida and para for female cases in Table I.

Table I was modified as requested.

3. In the pedigree it would be better if the phenotype could also be shown in addition to the genotype. This could be done by dividing each circle or square in two, one part showing genotype and the other half showing phenotype (affected or unaffected).

See comment to note 1 to Reviewer #1.

4. Please elaborate on reduced penetrance in previously reported cases with mutations in SPAST gene.

The issues of reduced penetrance were further commented in the revised manuscript (see page 6, In 2 from bottom).

5. Please discuss the possibility that IV-25 is still too young to manifest symptoms. The mean age of onset was 46.75 in the other patients, so it is possible that IV-25 might show clinical findings in the future.

See comment to note 4 to Reviewer #1.

6. English requires revision.

See comment to note 10 to Reviewer #1.

We hope that in this new dress the manuscript will be suitable for publication.

Sincerely,

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