Reviewer's report

Title: Frequency of SCA8, SCA10, SCA12, SCA36, FXTAS and C9orf72 repeat expansions in SCA patients negative for the most common SCA subtypes

Version: 0 Date: 25 Aug 2017

Reviewer: Hsiu-Chuan Wu

Reviewer's report:

The authors report in this manuscript that 441 ataxic patients, being negative for mutations in common SCA subtypes, were analysed for less common SCA-associated mutations such as non-coding regions of SCA8, SCA10, SCA12, SCA36 or other ataxia-associated mutations such as FMR1 and C9orf72. The results showed in their cohort that expanded repeats for SCA8 were detected in six patients, for FMR1 in eight, and for C9orf72 in one. The authors concluded that smaller number of the expanded repeats for FMR1 could be associated with the risk of developing neurological signs, whereas that for SCA8 could be a rare polymorphism and that for C9orf72 in their cohort did not broaden the phenotypic spectrum as the patient presented with dementia.

This manuscript conveys limited novelty as a considerable number of previous reports have addressed similar conclusion. The merit of this report mainly resides in a substantial number of the cohort which could add up to future systemic reviews. The description is generally easy to follow. There are, however, several concerns that might require further revision and clarification from the authors.

1. Abstract

* The authors are advised to specify the cohort is composed of 'unrelated' patients in Methods in Abstract, not until that in the main manuscript.

2. Introduction

* Several sentences in Introduction are far too long and complicated.

* The full description of abbreviations should be provided when the abbreviation is first mentioned. Then the authors are advised to use the abbreviation throughout instead of repeating the full descriptions again and again.
* The authors are advised to avoid descriptions in parentheses except abbreviations when first mentioned.

* Line 87: not suitable 'to detect' ==> should be 'for detecting'

* The rationale for analysing the hexanucleotide repeats in C9orf72 gene is vague here. As the authors only specify mutations in this gene are associated with FTD and ALD, not ataxia. Although increasing evidence has suggested a possible link between C9orf72 repeat expansion and cerebellar ataxia, the authors might want to intrigue the readers by shortly describing that in the Intro, not until the Discussion.

3. Methods

* The authors might want to clarify what 'other unspecific symptoms' means when describing the clinical presentations of their cohort.

4. Results

* Typo:

  SCA 8 ==> should be 'SCA8'

  TP PCR ==> should be 'TP-PCR' (there are few of them throughout the manuscript)

  Line 143: As for SCA8 ==> I suppose it should be SCA10

* The authors used 'SCA8' to describe this gene in Result section, whereas using ATXN8OS instead of the 'SCA8' (gene) in the Conclusion section when describing the RAN translation. The authors are advised to use one consistent gene name throughout.

* Although 6 patients had repeats greater than 83, the authors suggested none of them showed a pathogenic pattern. However in Result section in Abstract, the authors described these repeats are discussed to be (?) potentially pathogenic. The authors seemed to contradict themselves in deciding whether their result in SCA8 was pathogenic or not. Even in Discussion, they only mentioned that the established SCA8 pathogenic threshold is questionable. The authors might want to carefully clarify the definition of pathogenic pattern of SCA8 repeat expansion before drawing a clear conclusion from their results.

* Figure legend of figure 1 is missing.
* The authors are advised to organise the order of genes mentioned in Result section in Abstract in line with that in the main manuscript. Although this does not affect the conclusion at all, it indicates that the authors did not put sufficient effort into preparing their manuscript.

5. Discussion

* In order to improve the readability, the authors are advised to organise the order of genes mentioned in Discussion section in Abstract in line with that in the main manuscript. Alternatively, they can discuss the positive results first and then all negative results.

* Line 212, do the authors mean that SCA8 patients usually have other identified genetic causes for ataxia? Could the authors specify what these other genetic causes are and cite relevant references?

* C9orf72 vs C9ORF72. Italic vs normal font. The font should be italic for the name of genes and normal for that of proteins. The authors are advised to put more efforts in correcting these editing errors in their revision.

* Line 259: Beside ==> should be 'Besides', and there are several 'beside' in other parts of the manuscript.

6. Conclusion

* Far too long. It should be rewritten in order to be concise and clear. The authors tried to discuss the necessity of including SCA8 in the routine diagnostics for patients with ataxia but did not actually come to a conclusion. They then carried on discussing how RAN translation could be one of the molecular mechanisms for SCA8 repeat expansion. The authors have never mentioned RAN translation in their Discussion, why do they draw a conclusion here this mechanism might play a role in the inconsistent phenotypes of SCA8 repeat expansion? All these discussions should be shorten and moved to Discussion section.

* The authors mentioned that RAN translation has been reported in other nucleotide expansion disorders: DM1, FXTAS and C9ORF72. First of all C9orf72 is not a disorder, it's a name of a protein or gene, depending on the font. Secondly, RAN translation has been reported in C9orf72-related ALS/FTD, not all disorders related to mutations of this gene.
7. General concerns:

* A considerable number of sentences in the manuscripts are too long and complicated. It is therefore strongly recommended that this manuscript is checked by an English proofreading expert before submitting the revision. This is to ensure an accuracy in some texts and correct grammar usages.

* Editing error: typos, a consistent principle of using abbreviations, italic font for gene names, orders of genes mentioned in Result (both in Abstract and main manuscript) and Discussion

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited
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