Reviewer’s report

Title: Association between novel TARDBP mutations and Chinese patients with amyotrophic lateral sclerosis

Version: 1 Date: 23 September 2009

Reviewer: Rita Guerreiro

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The study by Xiong et al reports the screening of TARDBP in a Chinese cohort of 76 ALS patients, including 71 sporadic and 5 familial cases.

The sequencing analysis of the gene resulted in the identification of one novel mutation in a familial case (Ser292Asn). The authors present the clinical description of this proband and extend the analyses to other family members.

Ultimately, this study reports a new mutation in TARDBP and the associated phenotype. Although no definite conclusions can be reached regarding the pathogenicity of the mutation, the in silico analyses performed and the segregation data provided point towards the direction of this being a pathogenic mutation. In this way, the authors provide sufficiently accurate data to support most of the conclusions. Nonetheless, some points need to be addressed:

Major compulsory revisions

1. Although SIFT is a very easy to use in silico prediction software, it is not perfect. Authors should not assume the definite pathogenicity of a mutation based on the prediction form SIFT. Authors can say that the mutation found is most probably a pathogenic one, but it is incorrect to say that since SIFT predicted the variation to be deleterious to the protein function, this is a pathogenic mutation.

2. The authors should provide the correct nomenclature for all the mutations and polymorphisms at the coding and/or gene level, besides the protein level (for instance: 239-18t>C and Tyr374Term).

3. It is briefly referred in the abstract and methods sections that the studied patients do not have mutations in SOD1. Was this data published in a previous study? If so, a reference should be added.

Minor essential revisions

Title:

1. The term “mutations” (plural) implies that more than one mutation was found and associated with ALS.

Abstract:

2. “A homology search of the TDP-43 protein in different species demonstrated that it was highly conserved.” – is this sentence referring to the protein or to the mutation found?
Background:

3. Reference numbers should be provided for all the genes cited.

4. “These mutations affect the C-terminal region of TDP-43 may influence protein-protein interaction, exon skipping and splicing inhibitory activity, thus, may influence the proper function or transport of TDP-43.” should read: “…region of TDP-43 and may influence protein…”?

5. “Here, we first screened for TARDBP mutations in Chinese patients with ALS, and have identified one novel missense mutation, two silent mutations and one novel polymorphism.” – this sentence should be reformulated (does this mean that TARDBP was a first screen and something else was screened after?)

Methods:

6. “The sequence of the primers and the annealing temperatures are shown in the table.” – the table number should be provided in the text.

Results:

7. “One year later, he began to have some difficulty in using chopsticks and lifting his right arm…” should read “…his right arm”?

8. “Neurological examination showed muscle weakness involved all the extremities…” should read “…weakness involving all the extremities…”?

9. “…we speculated that Ser292Asn was from the dead and asymptomatic father.” – sentence should be reformulated for clarity.

Discussion:

10. Authors should further discuss the segregation data on the family: the mutation was found in four asymptomatic members beside the proband. The age at onset of the disease of the proband and the ages of these family members should be compared.

11. Authors should specify that studies by Gijselinck I et al and Guerreiro RJ et al failed to find mutations in sporadic ALS series.

12. “None of them is homogeneous” – this sentence is not clear within its context.

13. “The frequency of TARDBP mutations is 3.6% in FALS and 1.0% in SALS” – the authors should specify which population(s) these numbers refer to and provide a reference.

14. “Here, we have first screened the TARDBP mutations in Chinese patients…” – sentence should be reformulated for clarity.

15. “This frequency is much lower than those of previous studies, which may be due to the small sample size and the different races” – authors should re-write this sentence in order to clarify the following: 1) the frequency of mutations in a population does not arise from the size of the series studied (the probability of finding mutations does); 2) different races refer to different genetic backgrounds?

Discretionary revisions:

1. To avoid any misunderstanding, authors could use the term “mutation” when
referring to the Ser292Asn and the term “variant” when referring to the other non-pathogenic changes found.

2. In the results section, subsection “Clinical features of the FALS patient carrying Ser292Asn mutation”, the number of the proband in the pedigree (II.2) could be included.

3. Assumptions are made for the genetic status of individuals I.1 and II.5. The same could be done for individual II.3

4. “The authors also thank the anonymous reviewers for improving the manuscript.” – BMC Medical Genetics reviewers are not anonymous – this suggests the manuscript was previously submitted elsewhere.

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.