Reviewer's report

Title: High frequency of the TARDBP p.M337V mutation among south-eastern Chinese patients with familial amyotrophic lateral sclerosis

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Reviewer: Alessio Di Fonzo

Reviewer's report:

In this paper the authors performed a mutational analysis of TARDBP gene in seven families with ALS identifying a common known mutation that seems frequent in that region. They extended to 215 sporadic cases the study, sequencing the exon 6 only, where most of the TARDBP mutations lay and especially the one identified in familial cases described here. However none was found to carry the mutation. A synonymous variant, which was previously claimed to increase the risk of ALS, was detected in some sporadic patients.

The finding of this study is interesting, expanding the role of possible population specific mutations in ALS.

Major criticism:

It is quite difficult to follow the text, since English needs major revisions.

I have some suggestions:

Abstract:

Methods. I suggest to describe the genetic analyses performed and the population screened, for example: Seven index cases from ALS families negative for SOD1 and FUS mutations were screened by Sanger sequencing for TARDBP gene exon 2-6. 215 sporadic ALS patients were analyzed for TARDBP exon 6 only.

Results. Is not clear who is carrying the mutations identified. I suggest to indicate the number of index cases, from each family, that was found to carry a mutation.
More benign course compared with whom?

Main text
Sentence 1: I would change the sentence with: …. Selective neurodegeneration of both the upper motor neuron, and the lower motor neuron in brain stem and spinal cord. I think the sentence "until now, only few families were reported from China…” need a reference.

The sentence "In this study, / SOD1- and FUS. … has to be rewritten; it should be clearer who is carrying the mutation. If seven families have been studied, how it is possible that the mutation has been found in 5 families, and other 4 families? I suggest to indicate how many familial cases (intended as index cases, n=7) were found to carry the mutation, that would be more clear. Thereafter, the authors may explain how is cosegregating the mutation with ALS in other family members.

The authors may explain why SMN have been screened, since patients seems to show also sign of upper motor neuron degeneration, which is not typical of spinal muscular atrophy.

The older brother (II2) of the proband of family 3 (II4) died just three years after symptoms onset. I think that should be discussed, especially if the cause of death was related to ALS. Indeed, most of the patients described this paper carrying the mutation seem to have a longer course of the disease, but the short disease duration of case II2 may suggests a intrafamilial clinical heterogeneity.

I suggest to mention in the discussion a study were the p.G348C has been found in ALS and to compare the clinical feature of family 5 with those described so far (as the authors did for the M3337V mutation).

Figure: I suggest to indicate by an asterix which subject has been tested and if is carrying the mutation (mut) or not (wt)
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

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?
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Yes

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