Author’s response to reviews

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

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Author’s response to reviews:

Dear Editor and Reviewers,

We really appreciate all your comments and suggestions. Our responses are in blue below.

Reviewer reports:

Alessio Di Fonzo, Ph.D, M.D. (Reviewer 1): 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.

Response: Thank you for your reviewing. According to the reviewers’ suggest, we have rewritten some paragraphs. The revised manuscript has been edited by ‘American Journal Experts’.

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.

Response: Thank you for your suggestion. We have changed the sentence to the way you suggest.

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.

Response: Thank you. According to your suggestion, we have indicated the number of index cases from each family.

More benign course compared with whom?
Response: According to the literature, the survival for typical ALS patients was about 3-5 years after symptom onset. In this study, we observed that the patients carrying TDP43 p. M377V mutation have a long life survival (106.5±41.8 months), and also one mutation carrier was asymptomatic, so it indicated that a benign disease course.

Main text

Sentence1: 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.

Response: According to your suggestion, we have changed our expression.

I think the sentence "until now, only few families were reported from China…” need a reference.

Response: We have added the related 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.

Response: Thank you for your suggestion, and we haven’t expressed clearly. We have changed the expression in the revised manuscript. In this study, we screened 7 SOD1- and FUS- negative families, and found 5 families carried TDP43 gene mutations, and the other 2 families haven’t identified the disease-causing mutations. Besides, family1, family2, family 3 and family 4 carried the same c.1009A>G, p.M337V mutation, and the family 5 carried c.1042G>T, p.G348C mutation. We also have added the mutation in figure 1 and it confirmed the cosegregation 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.

Response: In clinic, some patients showed lower motor neuron dominant, and in our department, we screened the SMN and AR genes to excluded spinal muscular atrophy and spinal and bulbar muscular atrophy routinely. In the present study, some cases also manifested with lower motor neuron. So we detected the gene mutations in SMN gene routinely.

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.

Response: Thank you for your suggestion. We have further enquire about the disease course of the older brother (II2) and confirmed that he died from the respiratory failure. The short disease duration may suggest an intrafamilial clinical heterogeneity like you mentioned and we added related discussion in the revised manuscript.

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).

Response: Thank you for your suggestion. We have discussed the clinical features with p.G348C mutation in the revised manuscript.

Figure: I suggest to indicate by an asterix which subject has been tested and if is carrying the mutation (mut) or not (wt)
Response: Thank you for your suggestion. We have indicated in the figure 1 who is carrying the mutation (mut) or not (wt) according to your suggest.

Francisco Gondim, MD PhD FAAN (Reviewer 2): Xu et al. reported a high frequency of TARDBP mutations in familials ALS patients from Southeast Asia. Those patients had a trend for bulbar and upper limb involvement and a benign course, with prolonged survival.

Introduction:

1. Description of ALS should be more generally stated, and not confuse the general description with findings from TARDBP mutations (1st paragraph).

Response: Thank you for your suggestion. We have rewritten the first paragraph in introduction in the revised manuscript.

2. The last paragraph can be shortened since it is a summary of the abstract.

Response: Thank you for your reviewing. According to your request, we have rewritten the last paragraph in the revised manuscript.

Methods:

1. It would be important to provide more details about the recruitment and selection of the patients, so the reader can understand the epidemiological characteristics of the sample analyzed.

Response: Thank you for your suggestion. We have added the details about the recruitment and selection of the patients in the revised manuscript.
Results and Discussion:

Typos should be corrected throughout.

Response: Thank you for your reviewing. The revised manuscript have been edited by ‘American Journal Experts’.

It would be interesting to separate in the discussion the description of a comparison of the clinical and genetic variability of TARDBP mutations in Western and Asian patients.

Response: Thank you for your suggestion. Among different ethnic groups, due to different genetic background, patients with TDP43 gene mutations also showed highly clinical heterogeneity. We have added some literature about the clinical and genetic variability of TDP43 mutations in Western and Asian patients in the revised manuscript.


Title needs to be adapted to a complete sentence

Response: Thank you for your suggestion. We have changed the title to “High frequency of the TARDBP p.M337V mutation among Southeastern Chinese patients with familial amyotrophic lateral sclerosis”.

The authors describe their findings in this manuscript.

It is important for doctors to gain knowledge on this devastating disease. Therefore, a geno-phenotype relation is of importance for the clinic. Difficult however is to explain why fewer patients have been described in China compared to the rest of the world. The manuscript has
described the patients thoughtfully. However, structured description of the several cases in combination to their relatives is needed.

Response: Thank you for your suggestion. We also try to described the patient’s clinical features detailed. And according to your suggest, we described the main clinical features, including age at onset, site at onset, clinical phenotype, EMG test, survival et al. in table 1. However, due to some patients have died, the physical examination data could not be available. And according to another reviewer’s suggest, we also made some revision in the manuscript and figure 1.

In general, when major revisions (i.e. linguistic) are performed, perhaps the manuscript is suitable for publication.

Response: Thank you for your reviewing. According to you and other reviewers’ suggest, we have made a major revisions, and the revised manuscript have been also edited by ‘American Journal Experts’.