Author’s response to reviews

Title: Identification of VPS35 p.D620N mutation-related Parkinson’s disease in a Taiwanese family with successful bilateral subthalamic nucleus deep brain stimulation: a case report and literature review

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Author’s response to reviews:

September 3rd, 2017
Dr. Taku Hatano
BMC Neurology, Editor-in-Chief

RE: NURL-D-17-00389 (revised version 1),

Identification of VPS35 p.D620N mutation-related Parkinson’s disease in a Taiwanese family with successful bilateral subthalamic nucleus deep brain stimulation: a case report and literature review

Dear Dr. Hatano:

We would like to thank the reviewers for their helpful comments. Enclosed please find our revised manuscript. We have addressed the reviewers’ suggestions point-by-point as follow:
Reviewer 1: This paper is a first case report of the VPS35 mutation-related Parkinson's Disease case from Taiwan, also first report which was underwent STN DBS from Asian region. In the manuscript, the possibilities those VPS35 mutations are less in Asia, and the effect of STN DBS is high are mentioned. However, much of the content concerning about STN DBS is similar to the previous report,

Fleury et al.(14) cited by the authors. In order to improve this manuscript, please consider the following points.

Question 1: Did you measure intraoperative MERs for detecting STN and electrode implantation? If yes, were there any changes in STN activity compared to sporadic PD cases? Please note this point. I believe this information is useful for readers.

Reply: We thank the reviewer for the comments. We indeed measured the intraoperative microelectrode recording (MER) in STN during surgery. MER could identify the neuronal firing patterns of the STN and is the most commonly employed technique to assist and validate target localization. The recorded MER of our index patient was comparable with those with sporadic PD.

This point has been addressed in the “Case Presentation” section, page 5, lines 21-25.

Question 2: If you have any Brain CT scan or MR images taken after DBS implantation, please present key image as a figure.

Reply: We thank the reviewer for the suggestions. We have added the post-operational brain MRI in this revision as figure 1.

This point has been addressed in the “Case Presentation” section, page 5, lines 25; page 6, line 1/

Question 3: The authors presented long term follow up after STN DBS, however the outcome is similar previous report by Fleury et al.(14) The authors described that PD patients with genetical back ground seemed to receive much benefit from DBS as patients without genetical background. It is very interesting points. If possible, make another table containing comparison between three VPS35 mutant cases such as Taiwanese case, two Fleury's cases, and idiopathic PD cases such as STN DBS follow up studies, and discuss comparison. If LEDD reduction rate, UPDRS-III reduction rate was larger in VPS35 cases, it is a strong point to confirm authors' opinion.

Reply: We thank the reviewer for the helpful suggestions. We have added a table to compare the therapeutic effects of DBS in patients carrying VPD35 p.D620N mutation (our index patient and the two reported patients by Fleury et al) and 41 sporadic PD reported by Aviles-Olmos I et al.
The beneficial effects of STN-DBS were comparable in patients carrying VPD35 p.D620N mutation and patients with sporadic PD (Table 2). The surgery was done 10 years after onset of motor symptoms in average and the percentage of motor symptom improvement, scored by part III of UPDRS, was more than 30% in both group one year after surgery. The decreased dosage of LEDD maintained 5 years after surgery both in patients with and without VPD35 p.D620N mutation.

The results presented here contribute to the current understanding of STN-DBS treatment for genetically defined PD patients. Subjects carrying a PD-associated mutation seem to receive as much benefit from DBS surgery as patients without an apparent genetic background, suggesting that the indication for surgery should be based on the disease phenotype rather than its genotype. This point has been addressed in the “Discuss” section, page 9, lines 23-25; page 10, lines 1-4; and table 2.

Reviewer 2: In this manuscript the authors describe the finding of a VPS35 D620N mutation in a Taiwanese PD patient highlighting the good response to STN-DBS and the novelty of the presence of VPS35 mutations in that population. I have few minor remarks.

Question 1: Results: the number of Taiwanese controls from the WGS database Taiwan Biobank should be reported in the main text.

Reply: We thank the reviewer for the comments. Taiwan biobank contains the whole genome sequencing (WGS) database enrolling 997 Taiwanese people without known neurological disorders. This point has been addressed in the “Case Presentation” section, page 6, lines 22-25.

Question 2: Results: did the authors find any other rare variant within the genes of the NGS panel? has the duplication/triplication of SNCA gene been tested in this family with autosomal dominant PD? Reply: We thank the reviewer for the comments. We did not identify any rare variants, except VPS35 p.D620N, within the targeted genes from the NGS panel. The salsa multiplex ligation-dependent probe amplification (MLPA) kit P051-c1/P52-c1 (MRC-Holland, Amsterdam, The Netherlands) was used to detect large deletions or duplications of common PD-causative genes, including SNCA, Parkin, PINK1, DJ-1, ATP13A2, PLA2G6, FBXO7, DNAJC6 and LRRK2. The results of MLPA did not detect any genetic deletions or duplications of SNCA and other aforementioned common PD-causative gene.

This point has been addressed in the ”Case Presentation” section, page 7, lines 7-11 and lines 13-16.
Question 3: Fig.1: I suggest to report the age of onset of the affected individuals in the pedigree

Reply: We thank the reviewer for the comments. We have added the age of symptoms onset of the affected subjects in the pedigree, which was changed to be Figure 2 in this revision.

Question 4: Fig.2: The reverse complement electropherogram is not needed

Reply: We thank the reviewer for the comments. We have deleted the reverse complement electropherogram from the figure, which was changed to be Figure 3 in this revision.

Editor:

Thank you once again for giving us the opportunity to address the reviewers’ suggestions. We hope you would agree that with the revisions, the revised manuscript is much improved. The manuscript along with three figures and two tables was submitted according to the designated online submission process.

Thanks for your kind review of this paper.

Sincerely,

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