Peer Review File

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Reviewer A

This is an invited Editorial Commentary on a recent paper by Marks et al. which described the relationship between TMEM106B haplotypes with the pathological accumulation of TMEM106B C-terminal fragments (CTF) in postmortem tissue and their possible association with TDP-43 dysfunction.

The study was a significant one and worthy of commentary. However, there are a number of aspects of the review that could be improved.

1) The introductory sections that provide background on FTD (lines 19 – 62) unnecessarily long.
Reply: Thank you for the suggestion. These paragraphs were summarized.
Changes in the text: From lines 34 to 48, page 2.

2) The background section on TMEM106B (line 63 - 119) should be reorganized with the structure and function of the protein described in one paragraph and the relationship of the haplotype with disease risk in a separate paragraph. The protective effect of the minor allele in GRN mutation carriers (ref. 14) was the original and most important finding and should be more prominent. A separate paragraph should be devoted to the discovery of filaments composed of TMEM!06B C-terminal fragments.
Reply: We agree with your suggestion. The paragraphs were reallocated and a more prominent presentation of ref. 14 was included.
Changes in the text: From lines 68 to 120, pages 3-4; from lines 121-140, pages 4-5.

3) It should be emphasized that the immunohistochemical and immunoblot findings described by Marks et al. were previously reported in greater detail in papers by Perneel et al (ref. 7) and Vincente et al (Brain 2023).
Reply: These findings were highlighted.
Changes in the text: From lines 163 to 170, page 6; from lines 190-197, pages 6-7; from lines 204-220, page7.

4) The portions of the study that examined the association between TMEM106B CTF and other proteins (TDP-43) and pathways are the most novel. Even though they only provide soft evidence for a link to TDP-43, this is the section that deserves the greatest attention and the

most critical opinion.

Reply: Thank you for the suggestion. The change was included.

Changes in the text: From lines 221 to 242, pages 7-8.

5) There are numerous typos e.g., GNR (line 178), FLTD (line 187 and 194).

Reply: We corrected the mistakes.

Changes in the text: All the text.

6) Ref. 7 and 21 are the same.

Reply: Thank you. We excluded one of them.

Changes in the text: See reference list, lines 301- 390, pages 10-12, mainly ref 17.

7) The paper by Vincent et al (Brain 2023) should also be referenced in the discussion about the haplotype effect on immunoblot results.

Reply: The results from Vicente et al. were included.

Changes in the text: Lines 163-170, page: 6.

Reviewer B

The manuscript titled "Risk and progression of frontotemporal dementia in carriers of TMEM106B protective genotype and its relationship with TDP-43 pathology" effectively summarizes the work published by Marks et al., in Sci Transl Med 2024. However, I think the first portion of the editorial commentary could do a better job at describing the field and framing the context for the paper. Overall, I find that this is an interesting editorial that could be suitable for publication after some revisions. Please find more specific comments below:

Major edits:

1) In the first portion of the manuscript the language could be polished, and grammar could be better. Additionally, some of the concepts are repeated multiple times and other aspects of FTD are barely mentioned. Please revise line 19 to 119 to make it easier to read and more comprehensive of FTD in its manifestations. If at all available to the authors I would recommend reading and citing the Nature Reviews Disease Primers on Frontotemporal lobar degeneration by Grossman et al., 2023.

Reply: Thank you for the important suggestion. A native English speaker revised the manuscript. Moreover, the introduction was revised, in agreement with your commentary and Grossman et al was cited (ref 7).

Changes in the text: See overall changes, mainly lines 49-67, pages 2-3

2) In the initial part of the piece there is also a repetitive and disproportionate attention to diagnosis. Although true that diagnosis of FTD is challenging and an issue in the treatment of this disorder, the paper covered in this commentary does not talk specifically about diagnosis. Therefore, I would suggest to focus less on the diagnosis and more on other aspect of the disease such as the description of the pathology, which is instead relevant for the paper.

Reply: We changed the entire introduction (initial part).

Changes in the text: Lines 34-67, pages 2-3.

3) Please revise the language throughout the paper as there are areas that need improvement (i.e., line 138-142, 159-160, 225-227)

Reply: A native English speaker revised the manuscript

Changes in the text: See overall changes.

Minor edits:

1) Line 23: "The disorder is the second or third most common form of dementia before age 65" is it the second or the third? If there is contrasting evidence, please reference those that say second and those that say third.

Reply: The information was corrected.

Changes in the text: Lines 37-40, page 2.

2) Line 30 “its diagnosis is a challenging” doesn’t make sense

Reply: The phrase was deleted.

Changes in the text: Line 43, page 2.

3) Line 46 GRN the acronym needs to be spelled out

Reply: Corrected. Thank you!

Changes in the text: Line 224, page 7.

Reviewer C

This review highlights the relevant findings of the up-to-date literature about how TMEM106B genotypes associate with the risk of developing FTD-TDP. The article is well written. I suggest the following changes for improvement:

1. Subheadings of the different sections and a figure showing the structure of TMEM106B and eventually highlighting the main pathological features to help the reader's overview.
Reply: Thank you for the suggestion. According to the author guidelines, the text is unstructured, without subheadings. The figure 1 was included.
Changes in the text: Line 93, page 3.

2. The C9orf72orf expansion is not rare as FUS in FTD but is mentioned in the same sentence (Line 51)
Reply: The information was corrected.
Changes in the text: Line 66, page 3.

3. Often the authors say TMEM106B xxx is associated with e.g., cognition, please be more concise as the reader might be unfamiliar with the increased or decreased risk association. Please correct. (See Line 74 and 78)
Reply: We changed the paragraph, including more details.
Changes in the text: Line 75-85, page 3.

4. The word filament (Line 84) is not introduced. Only the term fragment in Line 70 and it is unclear what the authors refer to at this point.
Reply: The filaments compose the core of TMEM106B in brain tissue. The fragments are resulted by the proteolytic cleavage of TMEM106B.
Changes in the text: See overall changes.

5. Line 120 the journal and the expression "an elegant study" is not objective and should be deleted.
Reply: The expression was deleted.
Changes in the text: Line 141, page 5.

6. Line 154 should have an introduction for monomeric and dimeric protein and how the dimeric protein (homodimerization?) can be explained.
Reply: This mechanism is not completely elucidated. This information was included.
Changes in the text: Lines- 180-184, page 6.

7. The authors have not mentioned any neurochemical biomarker studies which measured TMEM106B in CSF/blood in FTD or related diseases (e.g., ALS) with the same pathology. Consider to include this in your review.

Reply: Few studies included TMEM06B as biomarkers due to its intracellular location. This information was included.

Changes in the text: 273-280, page 9.