RE: 207748-INS-RG-RV-2
"Dystonia in a Timothy syndrome mouse model uncovers an interaction between Ca^{2+} and metabolism"
Towers et al.

Dear Dr. Finkel and Eickelberg,

Below we provide our responses to the editorial directions as well as the reviewer responses. All of the editorial directions and reviewer queries are presented verbatim and our responses are presented in **bold and in red text**.

On behalf of all authors,
Geoffrey Pitt

I am pleased to inform you that we will accept your manuscript provided that you submit a revision that satisfactorily addresses the concerns raised in the reviews (appended below). We do not anticipate that this will necessitate further experimental data.

Your manuscript must also address the following items:

1. Ensure that the manuscript title conforms to the strictly enforced 15-word limit.
Confirmed.

2. Confirm that all author names are correct and complete. The published author list will appear as presented in your submitted Word document.
Confirmed.

3. Ensure that protein and gene symbols are formatted correctly and are consistent with NCBI Gene nomenclature. See Gene Nomenclature and Style for details: https://insight.jci.org/kiosks/publish/genestyle.
Confirmed.

4. Edit your abstract to state results from the completed study in past verb tense and general knowledge in the field in present verb tense.
Fixed.

5. JCI style does not permit claims of novelty unless they are qualified (e.g., what we believe to be novel). Please remove or qualify novelty statements in the abstract and text. Synonyms for novel (new, previously unknown, for the first time, etc.) must also be qualified or removed.
Fixed.

6. Per JCI style, statements of significance are limited specifically to statistical significance. Revise other instances to 'substantial', 'marked', or a similar synonym.
Fixed.

7. Figures are limited to 10 parts in total (e.g., parts A–J). Remove parts from your figures so that they adhere to this limit, and prepare the revised figures according to the journal's size and other formatting requirements. Note that there are no limits on the number of supplemental figures. Specifically, this applies to Figures 1 and 4.

All main and supplementary figures adjust accordingly.

8. For any individuals providing gifts of materials, specify the affiliation and location (including city) in Methods where appropriate.
n/a

9. Ensure that next-generation sequencing data have been deposited in a MINSEQE-compliant public database as appropriate, and provide the accession number in the Data Availability section of Methods in the main text of the manuscript. Please note, the data must be deposited and made public as a condition of acceptance.
n/a

10. In the Statistics summary, clarify whether Student's t test was 1- or 2-tailed, and specify that "A P value less than [X] was considered significant." Furthermore, clarify whether ANOVA was 1- or 2-way, if applicable.
Both 1- and 2- way ANOVA were used and are mentioned in statistics; use of each is specified in figure captions. T-test specified as 2-tailed in methods.

11. For all antibodies used, ensure that the source and catalog/clone number (in the case of commercial antibodies) or a description/reference to a description of the generation of custom antibodies is provided.
The company and catalog number for all antibodies are available in the methods.

12. Ensure that the source of all cell lines/animals used is indicated.
All commercial mouse lines are listed in the methods.

13. Move the following sections and collect them under the heading "Manuscript information" before "References": Author contributions, AI disclosure, Conflict of interest, Funding support, Acknowledgments, and Address for correspondence.
Done.

14. Authors must disclose the use of AI in research design as well as data extraction, analysis, and/or synthesis, including writing of the manuscript and preparation of figures, graphics, and other content. The disclosure should specify the task performed, the name and version of the AI tool, and the date or range of dates of use. If AI was not used, state ""The authors declare that no AI tools were used in the original research for or writing of this article."
Done.

15. If this work is funded partially or in full by the NIH, ensure that you have included a statement per the NIH Public Access Policy (https://insight.jci.org/kiosks/nih-access-policy) at the beginning of the Funding support section.
Done.

16. Edit your Funding support section according to Journal style: state sources of support in the form of grants as a list, providing all necessary information; for example, name of the funder(s), grant number(s), and recipient author(s) as appropriate. Include an NIH public access statement, if applicable.
Done.

17. Ensure that all references are present, there are no duplicates, and the reference list is formatted according to journal style (https://insight.jci.org/kiosks/publish/examples). We strongly

encourage use of EndNote in Microsoft Word to ensure that the format is correct. Furthermore, limit the use of URLs within the main text to citation of online databases and similar websites; if a URL refers to a publication, convert it to a numbered reference with complete bibliographic details.
Confirmed.

18. Confirm that you have provided supporting data values associated with the main manuscript and supplement material — including values for all data points shown in graphs and values behind any reported means — in a single Excel (XLS) file (distinct from any other supplemental material) using separate tabs for each applicable figure panel, with clear labeling for each tab. Ensure that the “Supporting data values” file is called out in the “Data availability” section in Methods.
Confirmed.

19. Please review the final version of the supplement that was included in your submission. The supplemental material will be published exactly as presented.
Reviewed.

20. Ensure that all figures are prepared according to journal style (https://insight.jci.org/kiosks/publish/figures); in particular, use 8 pt Helvetica or Arial font for labels, and avoid bold type. More detailed figure information is below:

All Figures:
-Remove all bold text from the images, including the labelling text.
-All text must be between 6 pt font minimum and 8 pt font maximum.
-Ensure that the figure legends indicate the statistical test for each applicable panel. For representative experiments, the figure legends should indicate the number of times the experiment was conducted.

Figure 1:
-This figure exceeds the part limit of 10, e.g., parts A–J.
-Confirm that this figure is presented on a portrait-oriented page.
Fixed. All figures are presented on portrait-oriented pages.

Figure 2:
-Confirm that this figure is presented on a portrait-oriented page.
Figure 2 fits on a portrait-oriented paged

Figure 3:
See "All Figures"

Figure 4:
-This figure exceeds the part limit of 10, e.g., parts A–J.
Fixed.

Figure 5:
-Confirm that this figure is presented on a portrait-oriented page.
-Patterns and textures make it difficult to read the data points on a bar graph. Bar graphs should be solid colors.
Fixed.

Figure 6:
-Confirm that this figure is presented on a portrait-oriented page.
Figure 6 fits on a portrait-oriented paged

If you have questions about these instructions, contact the Author Services Associate, Jessica Dishew (jdishew@the-jci.org).

Provide a point-by-point response to the reviewers' comments and a list of the incorporated changes at the beginning of your revised manuscript. Refer to https://insight.jci.org/kiosks/authors for information about manuscript preparation and publication fees.

We generally expect to receive revised manuscripts within two months. If you are unable to submit a revision within this period, please notify us.

Thank you for the opportunity to review this interesting work. We look forward to seeing the revised manuscript.

Sincerely,

Toren Finkel, MD, PhD
Deputy Editor
JCI Insight

and

Oliver Eickelberg, MD
Editor in Chief
JCI Insight

For the JCI Insight Editorial Board

Reviews

Reviewer A

The authors have adequately addressed my concerns. I have no further comments.

Reviewer B

The authors have addressed all of my major comments.

A few minor issues still need to be addressed:
1.Figure 1D and E: The figure caption needs to be corrected to read something like:
“(D, E) Latency to fall during the steady-state rotarod test (D, Mann–Whitney test, $p < 0.0001$) and (accelerating rotarod test (E, Mann–Whitney test).”
Updated former 1D,E, (now Figure 1C,D) accordingly.

2.Supplementary Figure 1: The error bars in panels J, L, O, and T do not appear to be reflected of the data points. Please confirm that the error bars are correct and accurately represent the reported variability.

Supplemental figure 2 (formerly supplemental figure 1) axis ranges have been fixed to display all data points on the plot. Error bars are correct, data points were unintentionally cutoff from axis limits.