Dear Editors,

We are writing to submit a revision of the manuscript NCOMMS-24-72394B: "Transcripts with high distal heritability mediate genetic effects on complex metabolic traits." We have completed the author checklist and made the requisite changes.

In this version there is a slight change in Figure 8D in the lower left panel. In collating the data files for the figures, we noticed that we hadn't seen that age was an available covariate in the study represented in Figure 8D (lower left panel). In the methods we stated that we regressed out these covariates. When we performed this adjustment the plot of the data changed slightly. This data collation also revealed that this study was composed of four technical replicates in each of three patients, rather than 12 independent patients. Thus, we changed the statistical test from a Welch's t test to a linear mixed model to better reflect the study design. We adjusted the figure legend and methods accordingly.

We are providing a summary not exceeding 250 characters for the e-alert. This statement is as follows: *High-dimensional mediation analysis in Diversity Outbred mice demonstrates the importance of distal gene regulation in the heritability of complex traits as well as the translatability of distal effects across mouse populations and human cohorts.*

Included in our submission are the following documents:

1. Cover letter

2. Manuscript file

3. Figure1 - Trait Overview

4. Figure 2 - Study Motivation

5. Figure 3 - HDMA Workflow

6. Figure 4 - Loading Interpretation

7. Figure 5 - Loading Heritability

8. Figure 6 - Tissues of Action

9. Figure 7 - CC-RIX Validation

10. Figure 8 - Human Translation

11. Supplementary File 1 - Supplementary Figures

12. Supplementary File 2 - Table of tissue-specific loadings

13. Supplementary File 3 - Table of CC-RIX strains and animal counts

14. Reporting summary

15. Editorial policy checklist

16. Completed author guidance form

The Source Data file was too large to include in this submission (566.6 Mb), so we have uploaded it to Figshare: https://figshare.com/account/projects/251795/articles/29247428?file=55154321

We thank the editors and reviewers for their careful reviews of this manuscript.

Sincerely,

Gregory Carter