Author’s response to reviews

Title: Reduced serum levels of pro-inflammatory chemokines in Fragile X Syndrome

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Author’s response to reviews:

Dear Editor,

We are submitting a novel version of our initial manuscript (MS# NURL-D-19-00686) entitled “Reduced serum levels of pro-inflammatory chemokines in Fragile X Syndrome” for consideration in BMC Neurology.

We thank the reviewers for their fair and thorough assessment of our initial manuscript. The modifications to the revised manuscript are detailed in the point-by-point response to the reviewers, appended to this letter.

Having now responded to all the points raised by both reviewers, we hope that this manuscript would now be suitable for publication in BMC Neurology.

Hoping that you will consider our manuscript for further reviewing, I remain, yours faithfully,

Laetitia Davidovic, PhD
Reviewer reports - Revision #2 (Minor)

Reviewer 1:
I have no further comment and happy with authors response. I am quite enjoy doing review for this paper.
### We appreciate that reviewer 1 is satisfied with our revised manuscript and thank him again for useful comments.

Reviewer 2: The authors have suitably addressed my concerns and I have no further requests for clarification or revision. As a matter of opinion (not requiring response), I remain somewhat unsatisfied by their description of the importance of the clustering approach; this is a focus of the paper (e.g., it's the last line of the abstract), but it is unclear what knowledge was gained. The clustering is useful in describing the underlying biology affected by FXS, as it provided additional information relative to the univariate comparisons, but it does little to inform the stratification of samples (as mentioned in the abstract/discussion). The clustering simply recapitulates the genetic diagnosis—we don’t need to guess diagnosis from a handful of immune markers, as we can objectively assess diagnosis with genotype. Had the clustering identifying subsets of the FXS sample, I would see support for the line of argument that these results are informative for the stratification of samples.
### We appreciate that Reviewer 2 has no further request and appears satisfied with our revised manuscript and thank him too for useful comments. In light of his last comment and as requested by the editor, we have nevertheless toned down our message regarding clustering by:
- removing the last sentence of the abstract (cf. p.2, ¶1)
- removing from the discussion the misleading sentence (cf. p.17, ¶1):
  “It paves the way for the use of K-sparse clustering analysis for the identification of combinations of disease biomarkers, but also for the stratification of patients in homogenous subtypes bearing similar biological patterns.”
- adding a sentence in the discussion (cf. p.17, ¶1) which explains that our study does not allow for the use of clustering to identify subtypes because of our small sample size, but that this approach would be amenable for larger samples:
  “Of note, the relatively small number of FXS patients included in our study (n=25) precluded us to use the clustering analysis to identify biological subtypes bearing similar cytokine patterns. However, K-sparse clustering could definitely be applied to larger samples to stratify patients in homogenous biological subtypes.”