

Peer Review File

Article Information: <https://dx.doi.org/10.21037/atm-24-86>

Reviewer A

The authors discuss in their manuscript the study design and results from Limone et al. study (Myeloid and lymphoid expression of C9orf72 regulates IL-17A signaling in mice). In the editorial text, authors discussed correctly the study design used to evaluate the potential role of C9orf72 in the effect of immune responses, including the immunophenotypic profile, hematopoietic progenitor cells and the regulation of cytokine signals in macrophages. Figure 1 is a nice representation of hematopoietic stem cells and progenitor populations. I have only a minor suggestion for authors to not include their abbreviation of "C9orf72" as "C9" in some parts of the manuscript.

RESPONSE: We thank the reviewer for the positive feedback. We made the requested amendment.

Reviewer B

This is an excellent review and perspective on the manuscript of Limone (2024) regarding C9orf72 function and biology.

RESPONSE: We thank the reviewer for the positive feedback.

Reviewer C

The paper is an extended summary of the article titled "Myeloid and lymphoid expression of C9orf72 regulates IL-17A signaling in mice" and therefore, it betrays the message of the title. It could be a commentary on that specific paper if the authors had done a more accurate job in searching the literature and providing real specific comments. The paper is divided into three sections and there is no abstract. The introduction, the summary and the conclusion, a heading would help. The introduction is brief, inaccurate and badly written. The summary is fine. However, the authors are not really making a comparison with the literature nor discussing the data accordingly. The conclusion does not match with the previous text, and take into account other pathologies. It appears that the aim of the authors is to provide a comparison of the relevance of the immune system in the three pathologies, specifically with AD. However, the comments are superficial and do not provide any real suggestions to the reader.

RESPONSE: We have extensively revised entire parts of our manuscript to address the concerns raised by this

reviewer. The revised sections are highlighted in blue text. We omitted to track the changes to avoid confusion.

- We have changed the title to better reflect the content, indicating a focused commentary on the role of C9orf72 in the immune system rather than a broad review on neuro-immune interactions.
- We have elected to use an unstructured text format for this manuscript, which is permitted according to the journal guidelines for manuscripts. The abstract is not required.
- We have expanded and re-wrote the introduction, adding more accurate and detailed information.
- A paragraph was added at the end of the summary section to place our work within the context of relevant literature.
- We restructured the conclusions to include more relevant literature and provide a deeper description of the immune system's role in other neurodegenerative diseases (NDs). This restructuring makes the commentary more complete, with detailed evidence on the neuroimmune crosstalk. These revisions enhance the overall coherence and relevance of our manuscript.

I am not suggesting here additional ways to improve the paper or articles to cite. I think it is the work the authors should have done.

RESPONSE: We appreciate the feedback and understand the importance of a thorough literature review and thoughtful commentary. However, we would like to emphasize that the peer review process is inherently collaborative, aiming to enhance the quality and clarity of scientific discourse. While we strive to conduct comprehensive literature searches and provide detailed analyses, constructive suggestions from reviewers are invaluable in guiding improvements and ensuring that the work meets the highest standards. The refusal to provide specific suggestions or articles to cite limits the collaborative spirit of the review process. Open communication and constructive feedback from authors and reviewers are crucial for advancing scientific knowledge and enriching the research community.