Review of: "Defining dysfunction due to loss of MECP2 in Rett Patient Brain"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

General comment

The paper by Korsakova et al. entitled “Defining dysfunction due to loss of MECP2 in Rett Patient Brain” describes the results of a single nuclei transcription profiling of neurons from the postmortem brains of Rett patients. Since MeCP2 regulates a large number of gene expressions by multiple mechanisms, a comprehensive understanding of altered gene expression in RTT patients is essential to define the neuropathology of RTT. The postmortem brain of patients is an excellent human sample for research. However, patient's brain tissue includes both wild-type and mutant cells, that limits accurate analysis. The authors succeeded in extracting the nuclei of neurons from the postmortem brain, separating wild-type and mutant nuclei by staining with MeCP2 and NeuN, and analyzing the transcription profiling. This method is a smart approach to utilize the patient's postmortem brain. Current data complement and support the other researches in RTT neuropathology.

Major comments

1. How should we understand the validity of gene expression profiling in the postmortem brain to define pathology in living patient's brain? Gene expression profiling will be highly dependent on brain activity. The profiling of the postmortem brain will strongly represent the situation before and after death of the patient. This may be different from profiling in the living patient's brain. These concerns or limitations of this methods should be mentioned in the discussion section.
2. There still seems to be a discrepancy between the transcription profile in the nucleus and the expression profile of proteins that actually function in the cell. The authors have confirmed protein expression for POU2F1/OCT1. However, the protein expression of many other transcripts analyzed in the nucleus remains unresolved. How do the authors approach this comprehensively and efficiently? This should be mentioned in the discussion section.

Minor comment

1. The brain contains a number of different neuron subtypes. Current studies primarily describe excitatory and inhibitory neurons. Did the postmortem brain sampling used here detect other subtypes, such as dopaminergic neurons?

2. The authors described "We found that activation of ATR was significantly increased upon UV induced DNA damage, and that MECP2+ and MECP2- neurons responded similarly to the damage (Figure 5A)." However, in Figure 5A, only wild type neuron's response are shown. Response of MECP2 negative neurons should be included.