Review of: "Multimodal Neuroimaging in Rett Syndrome With MECP2 Mutation"

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

The promising early diagnostic and therapeutic strategies for Rett syndrome based on non-human primate models

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Rett syndrome (RTT) is a progressive neurodevelopmental disorder primarily caused by mutations in methyl-CpGbinding protein 2 (*MECP2*) gene located on X chromosomes (Amir et al., 1999)[1]. Magnetic resonance imaging (MRI) is a unique technique to non-invasively detect the brain structure and functions *in vivo*. Recently, Kong et al (2022)[2] gave a comprehensive review for the multimodal neuroimaging researches for RTT with *MECP2* mutation in Journal of Frontiers in Neurology. The structural MRI studies revealed RTT showing global brain atrophy and specific regional gray matter reduction in the frontal, temporal, and dorsal parietal lobe, hippocampus, caudate nucleus, striatum, thalamus, midbrain, and cerebellum. RTT also showed reduced white matter (WM) microstructural integrity in left peripheral WM areas (including middle temporal, middle occipital, precuneus, and postcentral regions), left superior longitudinal fasciculus, sagittal stratum, corpus callosum and the bilateral cingulum bilaterally. Functionally, global and regional-specific abnormalities in cerebral blood flow, N-methyl-D-aspartate glutamate, gamma aminobutyric acid, benzodiazepine, and D2 dopamine receptors, ^{18}F-fluoro-L-dopa uptake, dopamine transporter, N-acetyl aspartate (NAA), total choline (Cho), Myo-inositol concentrations, and Cho/NAA, NAA/total creatine ratio in superior frontal gyrus, visual association areas of the occipital lobe, cerebellum, putamen, caudate nuclei, striatum, frontal, occipital and parietal lobes, insula, and hippocampus were found in individuals with RTT. Although these literatures revealed structural, molecular, and metabolic abnormalities in RTT, almost all these findings are based on cross-sectional studies and lack of longitudinal recordings to observe dynamic progression of the disease to identify specific neuroimaging characteristics in disease different stages for RTT, which may facilitate establishing therapy target for different clinical symptoms of RTT.

Although a few studies using*MECP2* knockout rodent models to investigate the brain dynamic developmental changes of RTT (Ricceri, De Filippis, & Laviola, 2008; Veeraragavan et al., 2016)[3][4], the rodent models are hard to well

mimic the clinical symptoms of RTT in human since intrinsic neurogenic and phenotypic differences (Chen et al., 2017; Novarino, 2017)[5][6]. Contrarily, the non-human primate showing similar phylogeny and brain structure and functions with human is an ideal model for human RTT (Chen et al., 2017)[5]. Using transcription activator-like effectors nucleases (TALENs) technique, we created *MECP2* mutant RTT monkey models and observed dynamic changes of brain structures and white matter tracts. We found reduced volume in left lingual gyrus, right lateral orbital gyrus, right inferior occipital gyrus, and bilateral parahippocampal gyrus at 8 months, in right inferior temporal gyrus at 8 and 20 months, in right occipital gyrus at 15 and 20 months, in right annectant gyrus, lingual gyrus at 20 months, and in left occipital gyrus at 8, 15, and 20 months in RTT monkeys (Chen et al., 2017)[5]. With diffusion tensor imaging, we explored the dynamical changes of WM microstructure and network topological architecture in 9 months, 16 months, 23 months, and 37 months RTT monkeys. We found whole brain diffusional and regional-specific microstructural abnormalities in splenium of corpus callosum, left posterior thalamic radiation, and right superior temporal gyrus in early stage of 9 months in RTT monkeys (Wang et al., 2021)[7]. No significant changes of WM microstructure in other periods were observed. Interestingly, although the WM microstructural lesion was only found in early stage of 9 months, the WM network topological architecture showed dynamic alterations from 9 to 37 months. Moreover, we further demonstrated that the WM microstructural properties could serve as effective biomarkers to distinguish RTT monkeys from wild type monkeys.

In spite of some achievements for RTT researches, to fully understand the neuropathology of RTT is still a long way. To delineate dynamic development changes of brain structure and function is essential to identify early biomarker for RTT diagnosis. In our previous studies, we have revealed reduced brain volume and disrupted WM microstructure even in early stage of 8 or 9 months in RTT monkeys. But whether the structural and functional abnormalities occurred earlier is still unclear. Using RTT monkey model, mapping the dynamic structural development from fetus to adult is potential to identify early neuroimaging biomarkers for RTT. Additionally, with the identified early neuroimaging biomarkers in non-human primate models to establish the cross-species diagnostic framework is demanded in future RTT research. In non-human primate or rodent RTT model, to validate the effectiveness of the model is mainly based on behavioral, blood transcriptomic profiling, or similar brain structural abnormalities in RTT in previous studies (Chen et al., 2017; Ricceri et al., 2008; Veeraragavan et al., 2016)[5][3][4]. Given RTT as a neurodevelopmental disorder, how to quantify the representational similarities between human and monkey RTT with brain imaging is promising. The objectively characterizing the effectiveness of animal models for human brain diseases may facilitate the development of this field. Moreover, with non-human primate RTT models, multi-omics fusion including macroscopic multimodal neuroimaging and microscopic genomics, proteomics, transcriptome, and single-cell sequencing may eventually reveal the neuropathological mechanism for RTT. Finally, given that on-human primate has similar phylogeny with human, which provide better references for drug development, gene and non-pharmaceuticals neuromodulation treatment for RTT than rodent models.

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