

Title: MeCP2 is critical for maintaining mature neuronal networks and global brain anatomy during late stages of postnatal brain development

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It is well established that mutations in the X-linked gene Methyl-CpG-binding protein 2 (*Mecp2*) cause Rett syndrome (RTT) at a specific postnatal stage. Although the mutation is present from birth, RTT syndrome in humans and mouse models is overtly manifest postnatally. The latency period to symptom initiation is about 12-18 months in human RTT girls, and 6-8 months in female afflicted mice, and approximately 5 weeks in the male mice. Recently, the Zoghbi, Bird and Ballas groups showed that loss of MeCP2 postnatally, even at adult stage, gave rise to the same spectrum of severe symptoms as when MeCP2 was lost at birth, suggesting that the primary requirement for MeCP2 in the brain occurs at a stage when many neuronal connections are already formed. The extreme dependence of MeCP2 at this late stage of brain maturity was surprising, so Dr. Ballas and colleagues sought to perform an in depth analysis of the abnormalities to help explain why the brain required MeCP2 at this stage.

The Ballas group compared the brain abnormalities in mice that had lost MeCP2 at both late juvenile (onset of classical RTT) and early adult stages. The abnormalities - small brain, compaction of neuronal cell bodies, reduced dendritic complexity and spine density - were similar at both stages, and similar to classical RTT, pointing to a regression of the mature brain in these situations to a less mature state. They also showed that the loss of MeCP2 resulted in significant reduction in a subclass of synaptic proteins, which could potentially lead to disruption of neuronal networks. Interestingly, the mRNA levels for these proteins were not changed in the mutant mice, suggesting that post-transcriptional mechanisms are likely involved in the regulation of these synaptic proteins by MeCP2, either directly or indirectly.

Together, these studies suggest that MeCP2 is required not only for continuous maturation of the brain at specific postnatal stage, but also for maintaining the mature neuronal networks past that stage. They could also help explain why girls born with *Mecp2* mutations start to regress after attaining normal developmental milestones, by demonstrating that in addition to developmental stagnation, the lack of MeCP2 can also induce regression of the existing neuronal networks.