

Title: Rett syndrome mutation MeCP2 T158A disrupts DNA binding, protein stability and ERP responses

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The Methyl-CpG-Binding Protein 2 (*MECP2*) gene was identified by Dr. Adrian Bird and his colleagues as a gene that encodes for the multi-functional MecP2 protein that regulates other genes during development. Mutation of the *MECP2* gene was identified as the cause of Rett syndrome by Dr. Huda Zoghbi and her laboratory in 1999. Since this seminal finding that links *MeCP2* and RTT, several genetically modified mouse models of RTT have been generated. These mouse models were analyzed to determine whether MeCP2 protein levels are tightly regulated to MeCP2 function, and indeed, a loss of MeCP2 does yield similar features of RTT found in humans. Despite the advances in genetic studies of RTT, the mechanisms by which dysfunction of MeCP2 leads to neurological symptoms remain poorly understood, and thus the development of therapeutics is delayed. In this article, Dr. Zhou and his colleagues describe a new mouse model for RTT designed to study a human mutation (T158A) in *MeCP2* that is associated with Rett syndrome.

Mutation of the Threonine 158 (T158) amino acid is one of the most frequent mutations observed in RTT, in which 10% of all RTT cases have a substitution of this Threonine to a Methionine amino acid (T158M) or to an Alanine amino acid (T158A). The amino acid T158 is located in the part of the MeCP2 protein that is responsible for binding DNA, and hence, its function to regulate other genes. Dr. Zhou developed genetically modified mice that carry a single targeted mutation of *MeCP2* at T158, converting Threonine to Alanine (T158A). Here, they carried out the phenotypic analyses of the *MeCP2 T158A* mouse model.

A careful comparison between the *MeCP2 T158A* mice and mice that completely lack *MeCP2* (*MeCP2-null*) was performed. These *MeCP2 T158A* mice also show similar characteristics to the previously reported *MeCP2-null* mice, although to a lesser extent. Overall, the *MeCP2 T158A* mice also mimic many aspects of RTT symptoms such as becoming more symptomatic with age, hindlimb clasping, and reduction in brain growth.

Dr. Zhou and colleagues have further characterized the *MeCP2 T158A* mice at the protein level of MeCP2, and found that it is a less stable protein. In fact, they show that this mutation results in a protein that does not bind DNA efficiently compared to unmodified MeCP2, and therefore the mutated MeCP2 protein does not regulate other genes at a normal capacity.

The *MeCP2 T158A* mutation mice were analyzed for imbalances in the neural network, which may cause many of the symptoms associated with Rett. The authors reported that there is an age-dependent disruption in the information processing of these mice, as measured by electroencephalogram (EEG) and event-related potentials (ERP) recordings for the brain's electrical activity. Correspondingly, it has previously been reported that EEG and ERP recordings are abnormal in individuals with RTT.

This study confirmed the causal role of the *MeCP2 T158* mutation in RTT. Their findings may lead to new strategies for therapeutic developments that may 1) to increase the binding affinity of MeCP2 T158A protein to DNA and 2) to increase the stability of MeCP2 T158A protein. Both of these strategies have the potential to restore MeCP2 function and are suitable for small compound screening in the future.

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