

13. MeCP2 Expression, Histone Acetylation, and Gene Expression in Rett Syndrome Frontal Cortex: Initial Examination

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Rett syndrome (RS) is associated in 65–80% of cases with mutations in the coding region of the transcriptional repressor MeCP2. Although MeCP2 most likely affects gene expression through chromatin changes secondary to recruitment of histone deacetylases, no data on histone acetylation in RS brain have been reported. This study intended to provide an initial examination of MeCP2 expression and histone acetylation in the frontal cortex from six RS subjects, four with (nonsense) and two without mutations, who have been characterized with transcription profiles by cDNA microarrays. Postmortem samples were evaluated by quantitative immunoblotting and compared with gender- and age-matched controls. Levels of acetylated histones H3 and H4 were compared with the number of abnormally regulated genes (>3 fold) per subject. In RS subjects, MeCP2's C-terminus immunoreactivity was decreased in both homogenates and synaptic fractions, and the 100 kDa/75 kDa ratio of MeCP2 was increased in synaptic preparations. Levels of the methyl-binding protein MBD1, but not MBD3, were elevated in RS samples. Levels of acetylated histones, in particular H3, were markedly increased in RS cortex. These levels correlated with the number of downregulated genes per RS subject. These data suggest that in RS cortex there is redistribution of MeCP2 and MeCP2-like expression, probably as a compensatory mechanism, and an increase in acetylated H3 as a major consequence of MeCP2 deficit. The preferential link between acetylated H3 and reduction in gene expression indicates that abnormal transcription in RS brain may involve the upregulation of other transcription factors and/or histone acetylation-independent mechanisms. Supported by HD 24448.