Loss of MECP2 Leads to Activation of P53 and Neuronal Senescence.

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Public Summary:
A cell culture model of Rett Syndrome was accomplished as a disease-in-a-dish. Skin cells from Rett Syndrome patients were reprogrammed to stem cells, and then further induced to become nerve cells. A set of cells were mutated in candidate genes for causing Rett Syndrome in order to confirm that this culture system could be used to provide further insight into this disease.

Scientific Abstract:
To determine the role for mutations of MECP2 in Rett syndrome, we generated isogenic lines of human induced pluripotent stem cells, neural progenitor cells, and neurons from patient fibroblasts with and without MECP2 expression in an attempt to recapitulate disease phenotypes in vitro. Molecular profiling uncovered neuronal-specific gene expression changes, including induction of a senescence-associated secretory phenotype (SASP) program. Patient-derived neurons made without MECP2 showed signs of stress, including induction of P53, and senescence. The induction of P53 appeared to affect dendritic branching in Rett neurons, as P53 inhibition restored dendritic complexity. The induction of P53 targets was also detectable in analyses of human Rett patient brain, suggesting that this disease-in-a-dish model can provide relevant insights into the human disorder.