Safety and efficacy of genetic *MECP2* supplementation in the R294X mouse model of Rett syndrome

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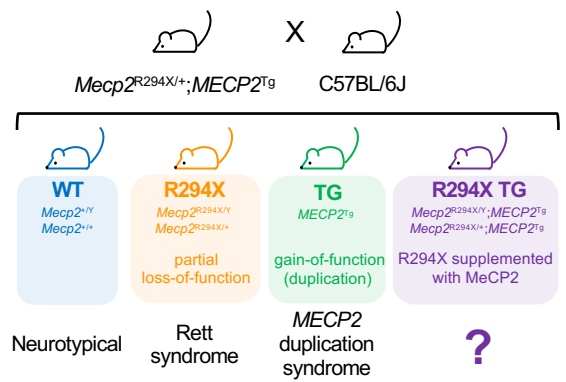
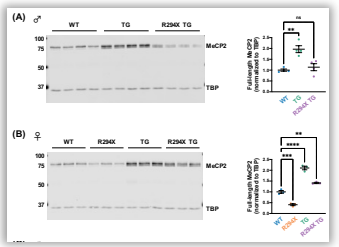
ABSTRACT

Rett syndrome is a neurodevelopmental disorder caused predominantly by loss-of-function mutations in *MECP2*, encoding transcriptional modulator methyl-CpG-binding protein 2 (MeCP2). Though no disease-modifying therapies exist at this time, some proposed therapeutic strategies aim to supplement the mutant allele with a wild-type allele producing typical levels of functional MeCP2, such as gene therapy. Because *MECP2* is a dosage-sensitive gene, with both loss and gain of function causing disease, these approaches must achieve a narrow therapeutic window to be both safe and effective. While MeCP2 supplementation rescues RTT-like phenotypes in mouse models, the tolerable threshold of MeCP2 is not clear, particularly for partial loss-of-function mutations. We assessed the safety of genetically supplementing full-length human MeCP2 in the context of the R294X allele, a common partial loss-of-function mutation retaining DNA-binding capacity. We assessed the potential for adverse effects from MeCP2 supplementation of a partial loss-of-function mutant and the potential for dominant negative interactions between mutant and full-length MeCP2. In male hemizygous R294X mice, MeCP2 supplementation rescued RTT-like behavioral phenotypes and did not elicit behavioral evidence of excess MeCP2. In female heterozygous R294X mice, RTT-specific phenotypes were similarly rescued. However, MeCP2 supplementation led to evidence of excess MeCP2 activity in a motor coordination assay, suggesting that the underlying motor circuitry is particularly sensitive to MeCP2 dosage in females. These results demonstrate that genetic supplementation of full-length MeCP2 is safe in males and largely so females. However, careful consideration of risk for adverse motor effects may be warranted for girls and women with RTT.

APPROACH

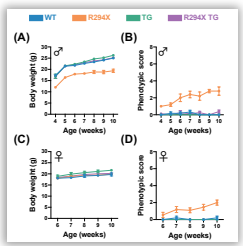


THE DATA



MeCP2 supplementation elevates full-length protein level in male and female R294X mice.

Gross RTT-like phenotypes are rescued in male and female R294X mice.



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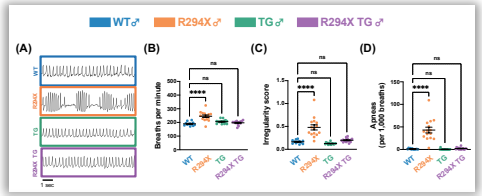
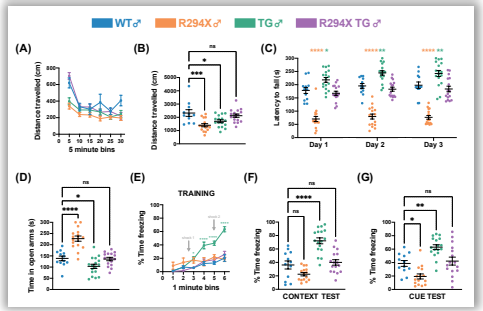
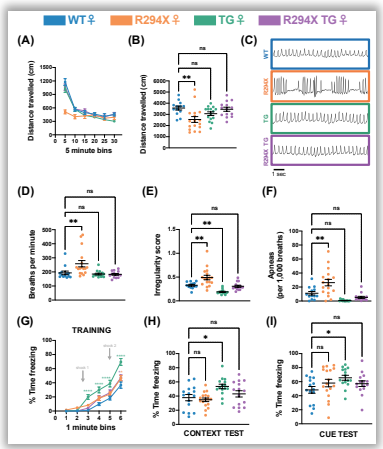
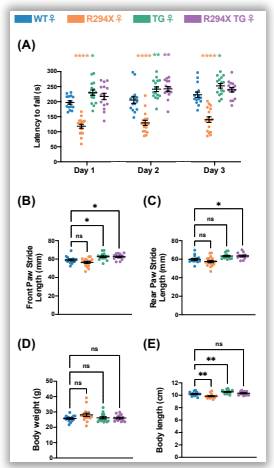




RTT-specific breathing phenotypes are rescued and bidirectionally dosage-sensitive behavioral phenotypes are normalized with *MECP2* transgene in male R294X mice.

RTT- and MDS-like behavioral phenotypes are rescued in female R294X mice.





Transgenic MECP2 supplementation leads to MDS-like motor coordination and gait phenotypes in female R294X mice.

CONC.

Genetic supplementation of MeCP2 in the context of the partial loss-of-function R294X mutation is safe and effective in males, and largely so in females. However, careful consideration of baseline motor function and risk for potential adverse motor effects with MeCP2 supplementation therapy may be warranted for girls and women with RTT.

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