Targeted RNA editing in brainstem alleviates respiratory dysfunction in a mouse model of Rett syndrome

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Keywords

neurological disorder, Rett syndrome, targeted RNA editing

Abstract

Rett syndrome is a neurological disease due to loss-of-function mutations in the transcription factor, Methyl CpG binding protein 2 (MECP2). Because overexpression of endogenous MECP2 also causes disease, we have exploited a targeted RNA-editing approach to repair patient mutations where levels of MECP2 protein will never exceed endogenous levels. Here, we have constructed adeno-associated viruses coexpressing a bioengineered wild-type ADAR2 catalytic domain (Editase^{wt}) and either *Mecp2*-targeting or nontargeting *gfp* RNA guides. The viruses are introduced systemically into male mice containing a guanosine to adenosine mutation that eliminates MeCP2 protein and causes classic Rett syndrome in humans. We find that in the mutant mice injected with the *Mecp2*-targeting virus, the brainstem exhibits the highest RNA-editing frequency compared to other brain regions. The efficiency is sufficient to rescue MeCP2 expression and function in the brainstem of mice expressing the *Mecp2*-targeting virus. Correspondingly, we find that abnormal Rett-like respiratory patterns are alleviated, and survival is prolonged, compared to mice injected with the control *gfp* guide virus. The levels of RNA editing among most brain regions corresponds to the distribution of guide RNA rather than Editase^{wt}. Our results provide evidence that a targeted RNA-editing approach can alleviate a hallmark symptom in a mouse model of human disease.