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Original Article

A high-fidelity RNA-targeting Cas13 restores paternal *Ube3a* expression and improves motor functions in Angelman syndrome mice

[redacted]

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Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by loss of function mutations in maternally expressed *UBE3A*. No gene-specific treatment is available for patients so far. Although intact and transcriptionally active, paternally inherited *UBE3A* is silenced by elongation of antisense long noncoding RNA *UBE3A-ATS* in neurons. Here, we demonstrated that RNA targeting of paternal *Ube3a-ATS* with a high-fidelity CRISPR-Cas13 (hfCas13x.1) system could restore *Ube3a* expression to similar levels as that of maternal *Ube3a* in the cultured mouse neurons. Furthermore, injection into lateral ventricles with neuron-specific *hSyn1* promoter-driven hfCas13x.1 packaged in adeno-associated virus (AAV-PHP.eb) could restore paternal *Ube3a* expression in cortex and hippocampus of neonatal AS mice for up to 4 months after treatment. Behavioral tests showed that expression of paternal *Ube3a* significantly alleviated AS-related symptoms, including obesity and motor function. Our results suggested that hfCas13x.1-mediated suppression of the *Ube3a-ATS* lncRNA potentially serves as a promising targeted intervention for AS.

Graphical abstract

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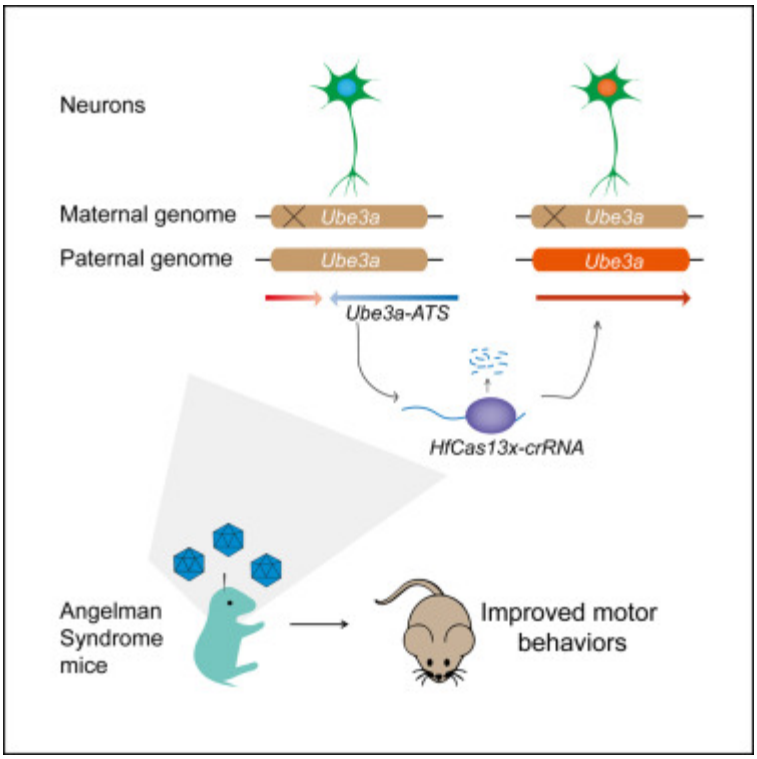

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Key Words

Angelman syndromeRNA editinghigh-fidelity Cas13paternal *Ube3a*motor function

Data and code availability

All RNA-seq data have been deposited in the NCBI SRA under project accession number PRJNA842160. Source data are provided in this paper.

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These authors contributed equally