Modular CRISPRa System for Tunable Transcription of FOXG1

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ABSTRACT

Researchers at the University of California, Davis have developed a modular CRISPR activation platform that enables precise upregulation of the haploinsufficient gene FOXG1 to address neurodevelopmental disorders without DNA cleavage.

FULL DESCRIPTION

This technology utilizes a split dCas9-based CRISPR activation (CRISPRa) system engineered with intein-mediated protein splicing to dynamically and specifically upregulate FOXG1 gene expression. The modular system allows swapping of transcriptional activators fused to N- and C-termini of dCas9, enabling tunable and synergistic gene regulation. Designed for efficient delivery via viral vectors such as AAV, it targets FOXG1 haploinsufficiency, (a cause of intellectual disability and severe neurodevelopmental syndromes), without inducing double-stranded DNA breaks, thus offering a potentially safer gene therapy alternative. The platform demonstrates robust elevation of both FOXG1 mRNA and protein in human cell lines and patient-derived neural stem cells and neurons, with no detectable off-target effects, and supports multiplexed sgRNA approaches for enhanced transcriptional control.

APPLICATIONS

- Gene therapy for FOXG1 syndrome and other neurodevelopmental disorders caused by haploinsufficiency.
- Development of treatment modalities for intellectual disability, autism spectrum disorders, epilepsy, and other brain-related conditions.
- Platform for tunable transcriptional activation therapies across a wide range of haploinsufficient genes.
- Research tools for studying gene dosage effects and transcriptional regulation in neurobiology and genetics.
- Potential expansion to gene therapies requiring precise, non-cutting gene expression modulation.
- Clinical application in patient-derived stem cells and neuronal models for personalized medicine.

FEATURES/BENEFITS

- Modular design enables flexible assembly of various transcriptional activator domains for optimized gene regulation.
- Split dCas9 with intein-mediated splicing overcomes AAV vector packaging size limitations, enabling delivery in size-limited viral vectors.

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OTHER INFORMATION

KEYWORDS

CRISPR activation, dCas9, FOXG1 syndrome, gene regulation, haploinsufficiency, modular system, neurodevelopmental disorder, sgRNA, transcriptional activator, viral vector delivery

CATEGORIZED AS

- **Biotechnology**
  - Genomics
- **Medical**
  - Disease: Central Nervous System
  - Disease: Genetic Diseases and

- Non-nuclease dCas9 avoids DNA cleavage, eliminating risks associated with double-stranded breaks and reducing the chance of genome alterations.
- Specific and efficient upregulation of FOXG1, with significant increases in protein levels, demonstrated in multiple relevant human cell types, including patient-derived neural stem cells and neurons.
- Demonstrated specificity with minimal off-target gene activation, confirmed by RNA sequencing and in silico analysis.
- Supports multiplex sgRNA strategies for fine-tuned and targeted gene activation, adaptable to other haploinsufficient genes and neurodevelopmental disorders.
- Provides a gene-size agnostic therapeutic strategy for genes unsuitable for traditional gene replacement, enabling modulation in non-dividing neuronal cells.
- Addresses haploinsufficiency disorders, specifically FOXG1 syndrome, and fills an unmet medical need for disease-modifying treatments of rare neurodevelopmental genetic disorders.

- Dysmorphic Syndromes
- Gene Therapy
- **Research Tools**
- Nucleic Acids/DNA/RNA

RELATED CASES

2025-557-0

PATENT STATUS

Patent Pending

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Reactivation of CDKL5 Using Epigenetic Editors
- Epigenetic Prevention and Treatment of CDKL5 Deficiency Disorder
- Exon-skipping Therapy for ADNP Syndrome
- Multiplex Epigenetic Editing using a Split-dCas9 System

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