Press Release

Keio University TOKYO MEDICAL UNIVERSITY

October 29, 2025
Keio University
Tokyo Medical University

Epigenome Editing Restores Gene Expression in Prader-Willi Syndrome

A joint research team led by the Keio University Regenerative Medicine Research Center, Keio University School of Medicine and Tokyo Medical University has succeeded in restoring the function of genes silenced in Prader-Willi syndrome (PWS; Note 1), a congenital imprinting disorder. Using patient-derived induced pluripotent stem cells (iPSCs; Note 2) and a CRISPR/Cas9-based epigenome editing system (Note 3), the researchers demonstrated that previously inactive maternal genes could be reactivated.

This groundbreaking achievement provides a novel therapeutic strategy at the molecular level for PWS, a disorder with no established curative treatment to date. The findings may also pave the way for new approaches to other imprinting disorders. The study was published in *Nature Communications* on October 28, 2025.

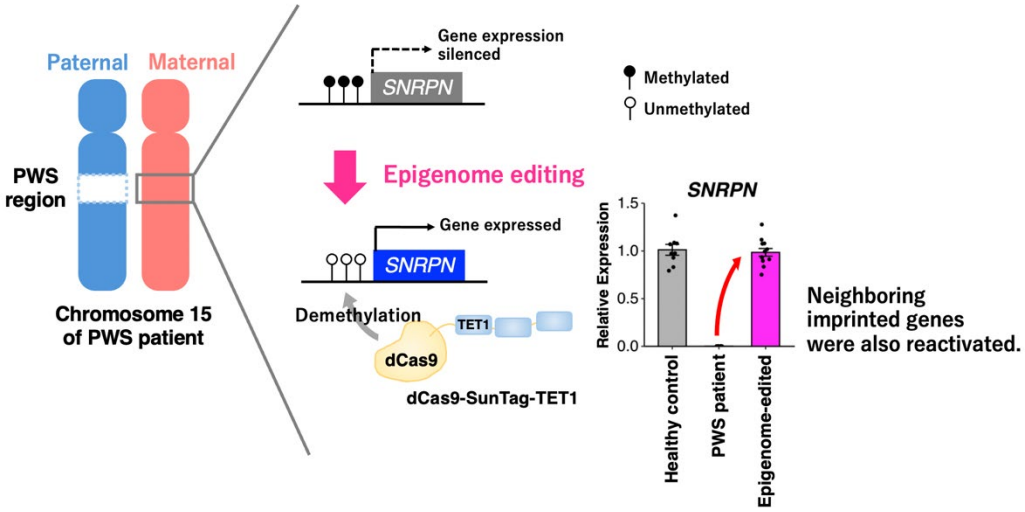

Figure: Reactivation of maternally silenced gene expression in PWS patient-derived cells by epigenome editing.

1. Main Points of Research

- Restored the function of genes silenced in Prader-Willi syndrome, a congenital imprinting disorder.
- Using patient-derived induced pluripotent stem cells, the researchers demonstrated that previously inactive maternal genes could be reactivated.
- Using a CRISPR/Cas9-based epigenome editing system, the researchers demonstrated that previously inactive maternal genes could be reactivated.
- Comprehensive methylation analysis visualized, at single-base resolution, widespread demethylation of previously inactive maternal genes.

2. Background of Research

Prader-Willi syndrome is caused by the loss of function of paternally expressed genes in a specific region of chromosome 15. Clinical manifestations include weak muscles (hypotonia), developmental delay, insatiable hunger (hyperphagia), obesity, and hormonal abnormalities, largely associated with hypothalamic dysfunction.

Although patients carry the same set of genes on the maternal chromosome, they are normally silenced by a phenomenon known as epigenetic regulation. Reactivating these maternal genes could potentially correct the underlying pathology. Previous approaches using small molecules to modify epigenetic status showed limited efficacy and carried risks of acting on unintended genetic off-targets effects. By contrast, CRISPR-based epigenome editing enables highly precise and locus-specific gene reactivation, offering a promising alternative.

3. Content of Research and Results

The research team applied the CRISPR/dCas9-Suntag-TET1 system to iPSCs derived from PWS patients and obtained the following results:

- Scientists successfully demethylated DNA at the imprinting control region of the maternal allele, leading to reactivation of silenced genes.
- Researchers observed that, once restored, gene expression remained intact after the manipulated cells differentiated into hypothalamic organoids—three-dimensional "mini-hypothalamus" structures generated from iPSCs that recapitulate or recreate appetite and hormone-regulating brain functions.
- The team conducted single-cell transcriptomic analysis, confirming a partial restoration of the abnormal gene expression patterns characteristic of PWS.
- Researchers did not detect significant off-target DNA methylation changes, supporting evidence for the potential safety of this approach.

This study is the first to demonstrate, in a human cellular model, the restoration of PWS-related gene expression through epigenome editing.

4. Future Developments

While this study represents a proof-of-concept using cellular and organoid models, it opens new avenues for future research:

- Validation studies using animals and studies of clinical applications to examine whether PWS symptoms can be improved.
- Research that applies this method to other imprinting disorders, such as Angelman syndrome and Russell-Silver syndrome.
- Studies to develop safe gene therapies, offering long-lasting and individualized interventions for patients and their families.

The research team for this study was supported by the Japan Agency for Medical Research and Development (AMED) and the Japan Society for the Promotion of Science (JSPS). The team will continue to carry out studies to bridge basic science and clinical application, aiming to deliver effective therapies for rare diseases.

5. Special notes

Note 1. Prader-Willi syndrome (PWS): A congenital disorder caused by the absence of paternally expressed genes on chromosome 15q11–13, leading to hypothalamic dysfunction that affects appetite and hormone regulation.

Note 2. Induced pluripotent stem cells (iPSCs): Artificially generated cells reprogrammed from somatic cells, capable of unlimited self-renewal and differentiation into virtually all cell types.

Note 3. CRISPR/Cas9 system: A cutting-edge gene-editing technology combining a DNA "scissor" enzyme with a guide RNA to precisely target and modify genomic regions.

Details of Journal Article

・Journal: *Nature Communications*
・DOI: 10.1038/s41467-025-64932-8

*Please direct any requests or inquires to the contact information provided below.

・Inquiries about research

Hideyuki Okano, Professor and Director, Keio University Regenerative Medicine Research Center.
Tel: +81-44-276-2387, +81-3-6629-3378, Email: hidokano@keio.jp

Hironobu Okuno, Assistant Professor, Department of Pediatrics and Adolescent Medicine, Tokyo Medical University / Visiting Lecturer, Center for Medical Genetics, Keio University School of Medicine / Research Associate, Keio University Regenerative Medicine Research Center
Tel: +81-3-3342-6111 (Ext. 5803) Fax: +81-3-3344-0643
Email: okuno.hironobu.6v@tokyo-med.ac.jp

・Inquiries about press release

Keio University Public Relations Office (Sagisaka)
Tel: +81-3-5427-1541 Fax: +81-3-5441-7640
Email: m-pr@adst.keio.ac.jp
University website: https://www.keio.ac.jp/

Tokyo Medical University Planning Division Public Relations Section
TEL: +81-3-3351-6141
Email: d-koho@tokyo-med.ac.jp
University website: https://www.tokyo-med.ac.jp/