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Potential drug appears to ease effects of Prader-Willi syndrome

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Duke Health researchers have identified a drug-like small molecule that, in animal experiments, appears to be an effective treatment for a genetic disorder called Prader-Willi syndrome.

Prader-Willi syndrome is characterized by poor feeding, growth and weak muscles in infancy, followed by excessive eating, obesity and behavioral problems in childhood. It occurs in about one of every 15,000 births and has no cure.

If the findings by the Duke-led team bear out in human studies, the drug could become the first treatment option for Prader-Willi syndrome. The concept proven in this study could also apply immediately to other similar type of genomic imprinting disorders in which children only inherit an active copy of a gene from one parent.

"Our findings are promising and indicate that we may have a path forward for the first time to treat the severe, life-limiting features of this genetic disorder," said Yong-hui Jiang, M.D., Ph.D., associate professor in Duke's departments of Pediatrics and Neurobiology. Jiang is senior author of a study published online Dec. 26 in the journal *Nature Medicine*.

In most cases of Prader-Willi syndrome, the responsible gene in the region of chromosome 15 from the father is missing and the mother's copy is silent. Jiang and colleagues focused their work on finding a way to activate the silent gene from the mother's chromosome to recover the

necessary gene function that would ordinarily be performed by the father's gene.

The researchers—including Bryan Roth, M.D., Ph.D, at the University of North Carolina at Chapel Hill and co-first authors Yuna Kim, Ph.D., and Hyeong-min Lee, Ph.D.—conducted screenings of more than 9,000 compounds. Using fluorescent marker in mouse embryonic fibroblasts, the researchers were able to see whether any of the small molecules triggered the cells to glow, which indicated they were capable of activating the maternal copy of the Prader-Willi gene.

A class of small molecule that are known as G9a inhibitors were successful, both in the mouse model of Prader-Willi syndrome and in human cells from patients with the disorder. G9a is an enzyme that is important for gene regulation.

The G9a inhibitors also appeared to have a therapeutic effect. When mice with Prader-Willi syndrome were treated with these small molecule drugs during infancy, they lived longer and had more normal growth.

"Our findings suggest that G9a inhibitors may play a role in regulating the silencing of parental chromosomes on certain genes that require an imprinting process for normal function," Jiang said. "This could provide a new insight for the molecular mechanism of genomic imprinting."

In addition to Jiang, Kim, Lee and Roth, study authors include Yan Xiong, Noah Sciaky, Samuel W. Hulbert, Xinyu Cao, Jeffrey I. Everitt and Jian Jin.

More information: Targeting the histone methyltransferase G9a activates imprinted genes and improves survival of a mouse model of Prader–Willi syndrome, *Nature Medicine*, nature.com/articles/doi:10.1038/nm.4257

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