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Rare obesity syndrome therapeutic target identified

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Columbia University Medical Center (CUMC) researchers have discovered that a deficiency of the enzyme prohormone covertase (PC1) in the brain is linked to most of the neuro-hormonal abnormalities in Prader-Willi syndrome, a genetic condition that causes extreme hunger and severe obesity beginning in childhood. The discovery provides insight into the molecular mechanisms underlying the syndrome and highlights a novel target for drug therapy.

The findings were published online today in the *Journal of Clinical Investigation*.

"While we've known for some time which genes are implicated in Prader-Willi syndrome, it has not been clear how those mutations actually trigger the disease," said lead author Lisa C. Burnett, PhD, a post-doctoral research scientist in pediatrics at CUMC. "Now that we have found a key link between these mutations and the syndrome's major hormonal features, we can begin to search for new, more precisely targeted therapies."

An estimated one in 15,000 people have Prader-Willi syndrome (PWS). The syndrome is caused by abnormalities in a small region of chromosome 15, which leads to dysfunction in the hypothalamus—which contains cells that regulate hunger and satiety—and other regions of the brain. A defining characteristic of PWS is insatiable hunger. People with PWS typically have extreme obesity, reduced growth hormone and insulin levels, excessive levels of

ghrelin (a hormone that triggers hunger), and developmental disabilities. There is no cure and few effective treatments for PWS.

Dr. Burnett and her colleagues used stem cell techniques to convert skin cells from PWS patients and unaffected controls into brain cells. Analysis of the stem cell-derived neurons revealed significantly reduced levels of PC1 in the patients' cells, compared to the controls. The cells from PWS patients also had abnormally low levels of a protein, NHLH2, which is made by NHLH2, a gene that also helps to produce PC1.

To confirm whether PC1 deficiency plays a role in PWS, the researchers examined transgenic mice that do not express Snord116, a gene that is deleted in the region of chromosome 15 that is associated with PWS. The mice were found to be deficient in NHLH2 and PC1 and displayed most of the hormone-related abnormalities seen in PWS, according to study leader Rudolph L. Leibel, MD, professor of pediatrics and medicine and co-director of the Naomi Berrie Diabetes Center at CUMC.

"The findings strongly suggest that PC1 is a good therapeutic target for PWS," said Dr. Burnett. "There doesn't seem to be anything wrong with the gene that makes PC1—it's just not getting activated properly. If we could elevate levels of PC1 using drugs, we might be able to alleviate some of the symptoms of the syndrome."

"This is an outstanding example how research on human stem cells can lead to novel insight into a disease and provide a platform for the testing of new therapies," said Dieter Egli, PhD, a stem cell scientist who is an assistant professor of developmental cell biology (in Pediatrics) and a senior author on the paper.

"This study changes how we think about this devastating disorder," said Theresa Strong, PhD, chair of the scientific advisory board of the

Foundation for Prader-Willi Research and the mother of a child with PWS. "The symptoms of PWS have been very confusing and hard to reconcile. Now that we have an explanation for the wide array of symptoms, we can move forward with developing a drug that addresses their underlying cause, instead of treating each symptom individually."

Following the findings reported in this paper, the Columbia research team began collaborating with Levo Therapeutics, a PWS-focused biotechnology company, to translate the current research into therapeutics.

The study is titled, "Deficiency in prohormone convertase PC1 impairs prohormone processing in Prader-Willi syndrome."

Provided by Columbia University Medical Center