Nature Reviews Endocrinology | Published online 23 Feb 2018; doi:10.1038/nrendo.2018.19

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GENETICS

Functional link to hyperphagia in PWS

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A recent study published in *The Journal of Clinical Investigation* has unravelled the role of hypothalamic *Snord116* in the hyperphagia that is characteristic of Prada–Willi syndrome (PWS) using a new mouse model of the disease. Previous studies have implicated the deletion of *SNORD116* in PWS in humans, but the functional link between *SNORD116* and hyperphagia in PWS has remained unclear, until now.

“We wanted to understand how *SNORD116* was functionally linked to the dysregulated energy homeostasis evident in PWS and so set out to study the neural mechanisms in the mouse,” says co-corresponding author Giles Yeo. “However, while humans with a deletion of *SNORD116* become obese and hyperphagic, these phenotypes do not arise in mice with a congenital *Snord116* deletion; these mice are small, similar to the early failure to thrive in human patients with PWS, but they never transition to obesity.”

The authors hypothesized that by deleting *Snord116* in the mediobasal hypothalamus of adult mice that did not have an early growth phenotype they would be able to uncover a metabolic or food intake phenotype. They created an adult-onset hypothalamic deletion of *Snord116* mouse model by injecting adeno-associated virus (AAV)–Cre into the mediobasal hypothalamus using a stereotaxic frame. This approach enabled Yeo and colleagues to study the functional consequences of *Snord116* deletion, thus linking loss of *Snord116* to hyperphagia.

“Mice with an adult-onset hypothalamic deletion of *Snord116* were demonstrably hyperphagic and some also developed obesity, which highlights the role of hypothalamic *Snord116* in the hyperphagia of PWS,” adds Yeo. “Interestingly, we did not observe changes in the expression of genes that control hypothalamic melanocortin or pro-hormone processing after deleting *Snord116*, which suggests that these hypothalamic energy homeostasis pathways remain intact in our mouse model.”

The authors now plan to refine their mouse model to avoid the need for stereotaxic surgery. As hyperphagia in PWS is without effective pharmacological therapies, the authors hope that in the future this model will be useful as a preclinical model that can be used to test interventions.

Alan Morris

ORIGINAL ARTICLE Polex-Wolf, J. *et al.* Hypothalamic loss of *Snord116* recapitulates the hyperphagia of Prader–Willi syndrome. *J. Clin. Invest.* https://doi.org/10.1172/JCI97007 (2018)