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Worms reveal new role for hormones in Bardet-Biedl syndrome

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A new study, conducted by researchers at the University of California, San Francisco, has shed new light on a genetic disease known as Bardet-Biedl syndrome (BBS)—a condition in which patients show mental and developmental delays, short stature, early onset blindness, extra digits on the hands and feet, kidney abnormalities and obesity. While the occurrence of BBS is rare—occurring in roughly 1 in every 150,000 live births—scientists believe that by understanding the mechanisms of function of BBS genes and their protein products they will gain insights into molecular processes that control development, vision, kidney function and obesity.

Following the identification of mutations that cause BBS, scientists had discovered that a set of these genes encode for a protein complex that is required for the proper functioning of cilia, antenna-like structures found on the surfaces of many cells. Like antennae, cilia are important for communication between cells as many proteins that facilitate cell-cell communication signals are localized to these structures.

In the new article, published December 13 in the online, open-access journal *PLoS Biology*, UCSF researchers report their discovery that mutations in BBS genes not only control incoming communication via the antenna-like cilia but also outgoing communication via the release of hormones. The researchers—led by Dr. Kaveh Ashrafi, associate professor in the UCSF Department of Physiology and a member of UCSF Cardiovascular Research Institute and the Diabetes Center—took advantage of the fact that counterparts of BBS genes are also found in

the small roundworm Caenorhabditis elegans. Despite the obvious differences between these microscopic worms and humans, numerous basic mechanisms that underlie cellular and animal physiology work in similar ways in these evolutionarily distant organisms.

Reminiscent of some of the symptoms seen in BBS patients, the mutations in the corresponding C. elegans genes lead to smaller size, abnormal feeding behavior & metabolism, and sensory defects. In the course of analyzing bbs mutant C. elegans, the researchers made an unexpected finding that these mutant animals have abnormally high levels of hormonal release. By blocking this excess release in the bbs worms, but without correcting defects in the cilia, the UCSF researchers found that they could restore normal body size, feeding, and metabolism to the worm.

"Good communication is key to any relationship, and cells are no exception," said Dr. Ashrafi. "This work expands understanding of molecular roles of BBS proteins and suggests that excessive hormonal release could underlie some of the symptoms seen in BBS patients, and thus opens up therapeutic avenues. Of course, we are a long way from knowing that for sure in human. While it is natural to consider all of the complexities of human physiology, it is precisely the simplicity of C. elegans and its amenability to experimentation that is helping us to learn the basic functions of some human disease genes."

More information: Lee BH, Liu J, Wong D, Srinivasan S, Ashrafi K (2011) Hyperactive Neuroendocrine Secretion Causes Size, Feeding, and Metabolic Defects of C. elegans Bardet-Biedl Syndrome Mutants. *PLoS Biol* 9(12): e1001219. doi:10.1371/journal.pbio.1001219

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