Sex-specific behaviors traced to hormone-controlled genes in the brain

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Hormones shape our bodies, make us fertile, excite our most basic urges, and as scientists have known for years, they govern the behaviors that separate men from women. But how?

Now a team of scientists at the University of California, San Francisco (UCSF) has uncovered many genes influenced by the male and female sex hormones testosterone and estrogen that, in turn, govern several specific types of male and female behaviors in mice.

The UCSF team selectively turned many of these genes off one by one and found they could manipulate individual behaviors in the mice, like their sex drive, desire to pick fights, or willingness to spend extra time caring for their young.

"It's as if you can deconstruct a social behavior into genetic components," said Nirao Shah, MD, PhD, an associate professor in the Department of Anatomy at UCSF who led the research, which is published in the 2/3/12 issue of the journal *Cell*. "Each gene regulates a few components of a behavior without affecting other aspects of male and female behavior.

In addition to illuminating the role of genes in male and female behavior, Shah said, the results also have greater implications: If male and female behaviors can be broken down into individual component parts, what other complex behaviors could similarly be deconstructed?

Identifying how genetic differences in our brains account for the differences in our behavior may also be a starting point for understanding how to better address human mental illness and neurodegenerative conditions in which such gender differences exist. For example, autism is four times more common in males than in females.

"Some of the genes we have identified in our study have indeed been implicated in various human disorders that are found in sex-skewed ratios," said Shah. "We won't immediately find all the answers to these disorders based on this research alone, but in the future, it might indeed help to identify more informed ways of treating such conditions."

Hormones, Sex, and Society

Scientists have known for years that hormones exert a profound control over male and female biology. They influence whether an embryo develops into a male or female fetus. They kick in during puberty and promote gender-specific characteristics, such as facial hair in men and breasts in women. They also stimulate the production of male sperm and female ova.

These actions have led to the widespread use of hormones in mainstream and fringe medicine for years. A major part of sexual reassignment procedures involves the long-term administration of hormones like estrogen or testosterone. Athletes seeking a competitive edge and middle-aged men seeking to prolong the vigor of youth sometimes use testosterone—often inducing aggressive behavior in the process.

While the connection between sex hormones and behavior has been known for years, scientists have only recently made significant headway in demonstrating how profoundly one affects the other by altering the levels of male and female hormones in laboratory animals.

Female mice in the laboratory normally exhibit what one might consider classic motherly behaviors—mating with male mice and nurturing their young. But female mice with a genetic trait making them unable to sense the hormone estrogen lose their interest in sex and spend less time caring for their offspring.

Fortified by testosterone, male mice in the laboratory display behaviors tending toward the aggressive. They will fight with each other, try to mount female mice and mark their territory with urine. Deprived of testosterone, however, castrated male mice no longer behave so aggressively.

Scientists have long suspected that sex hormones ultimately influence gene expression in the brain-. About six years ago, Shah and his colleagues set out to find such genes by using DNA microarrays, a routine laboratory assay, to analyze sex differences in gene expression in the hypothalamus, a region of the brain known to be involved with hormone sensing.

They found 16 genes that were expressed differently between males and females in the hypothalamus and showed that such differences were regulated by sex hormones. But in identifying these 16 genes, Shah and his colleagues also discovered they could tease apart classic, male and female hormone-driven behaviors into individual elements—each governed by its own genes.

The situation is analogous to the way a house draws its power from the grid. A sex hormone is similar to the main breaker that connects the house to the utility pole and regulates electricity to the entire house.

Individual genes influenced by sex hormones are like the light switches in each room, making it possible to turn the lights on in the kitchen while leaving the bedroom dark.

Sex and Behavior—More than the Sum of Parts?

Much like a main electrical box with many breaker switches, male and female behaviors are actually made up of many behaviors, like sex drive or an inclination to fight. Shah and his colleagues demonstrated this by manipulating the genes separately, sometimes with drugs, to turn them off.

Specifically, they showed that they could selectively knock out some male behaviors so that males continued to fight and mark territory normally but altered their mating routine with females. Likewise they could modulate female mouse behaviors to make them maintain active interest in sex but spend less time caring for their young, or vice versa.

"Other components of male and females behaviors appeared unchanged," Shah said. The implications of this simple observation that a complex human behavior may be composed of numerous genetically controlled elements are both intriguing and daunting, he added. Moreover, it is likely, Shah said, that there are many additional genes that will be discovered to be sex hormone regulated that, in turn, control other components of male or female behaviors.

More information: Xu et al.: “Modular genetic control of sexually dimorphic behaviors.” *Cell*, DOI:10.1016/j.cell.2011.12.018

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