Genetic tug of war in brain subregions influences parental control over offspring behavior

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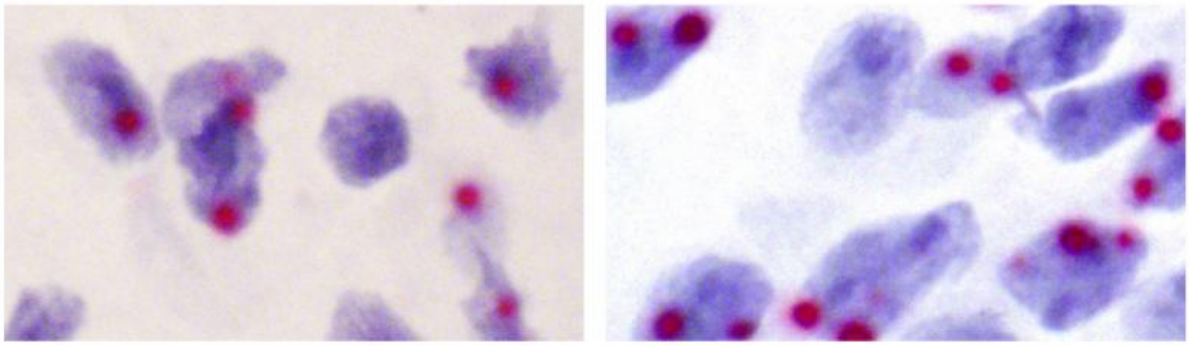

Typically genes express two copies, one from the mother and one from the father. Genomic imprinting is a mechanism that allows for parental control over gene expression: the copy from one parent is expressed while the other is silenced. Researchers at the University of Utah School of Medicine report a targeted version of genomic imprinting in mice that is more common than classic imprinting. Published in *Cell Reports*, so-called noncanonical imprinting is particularly prevalent in the brain, and skews the genetic message in subpopulations of cells so that mom, or dad, has a stronger say. The left figure shows a subset of brain cells that predominantly express a single copy of the autism-linked gene *Ahi1* inherited from one parent (one dot). The right figure shows a subset of brain cells that express both parents' copies of *Ahi1* (two dots). Brain cell nuclei are counterstained in blue. Targeted, noncanonical imprinting may be the preferred strategy over silencing one parental gene copy in every tissue. Credit: Christopher Gregg, University of Utah

Not every mom and dad agree on how their offspring should behave. But in genetics as in life, parenting is about knowing when your voice needs to be heard, and the best ways of doing so. Typically, compromise reigns, and one copy of each gene is inherited from each parent so that the two contribute equally to the traits who make us who we are. Occasionally, a mechanism called genomic imprinting, first described 30 years ago, allows just one parent to be heard by completely silencing the other.

Now, researchers at the University of Utah School of Medicine report on a version of genetic parental control in mice that is more targeted, and subtle. Published in *Cell Reports*, so-called noncanonical imprinting is particularly prevalent in the brain, and skews the genetic message in subpopulations of cells so that mom, or dad, has a stronger say. The mechanism can influence offspring behavior, and because it is observed more frequently than classic imprinting, appears to be preferred.

"The field has traditionally thought of genetics at the level of the whole animal, and sometimes the tissue. We're documenting it at the cellular level," says senior author Christopher Gregg, Ph.D., assistant professor of neurobiology and anatomy. "Genetics is much more complicated than we thought."

A case in point is the impact of noncanonical signaling on motivated behaviors that prompt a timid mouse to leave its protective shelter when it needs to search for food. Five genes preferably controlled by mom, or dad, cluster within a biochemical pathway that creates serotonin and dopamine, neurochemicals that affect mood and behavior. The imprinting appears to be further customized to influence behavior by being enriched in subregions of the brain known to control it (arcuate nucleus, and dorsal raphe nucleus). When the scientists remove the active, maternal copy of one of the genes, tyrosine hydroxylase (Th), they see a modest but consistent increase in the amount of time the mice

spend out in the open. By contrast, mice with their muffled, paternal copy removed show no behavioral changes.

"We speculate that a better strategy for imprinting is to do it in the cells that are needed to achieve the desired effect, rather than to do it in every tissue," says Gregg.

In total, 80 percent of 210 imprinted genes analyzed - the vast majority - were subject to noncanonical imprinting. 64 percent of those genes showed parental bias exclusively in the brain or subregions of the brain, and not in non-neural tissues, liver or muscle.

A novel method that visualizes active copies of genes shows that the bias stems from differences within populations of cells. While canonically imprinted genes have just one active copy in nearly every cell examined, noncanonically imprinted genes have one active copy in subsets of cells, and two active copies in others.

The results expand on previous work by another group who found a gene that imprints in specific neurons, and is reported to be associated with autism when mutated. This and the current study's behavior experiments highlight that in addition to fine-tuning parental control, noncanonical imprinting may have a downside.

Gregg speculates that the targeted form of imprinting gives rise to "high-risk" neurons that are especially vulnerable to mutations inherited from one parent because they don't express a second, healthy back-up copy to compensate for the mistake. "We think that subpopulations of cells that preferentially express mutated genes could disproportionately contribute to brain disorders such as autism," he says. Future research will test the hypothesis and novel therapies to overcome the deficits.

More information: "Noncanonical genomic imprinting effects in

offspring" by Paul Bonthuis, Wei-Chao Huang, Cornelia Stacher Hörndli, Elliott Ferris, Tong Cheng, and Christopher Gregg, will be published in *Cell Reports* online, July 30, 2015

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