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In the Brain, Many Genes Biased Toward One Parent's Influence

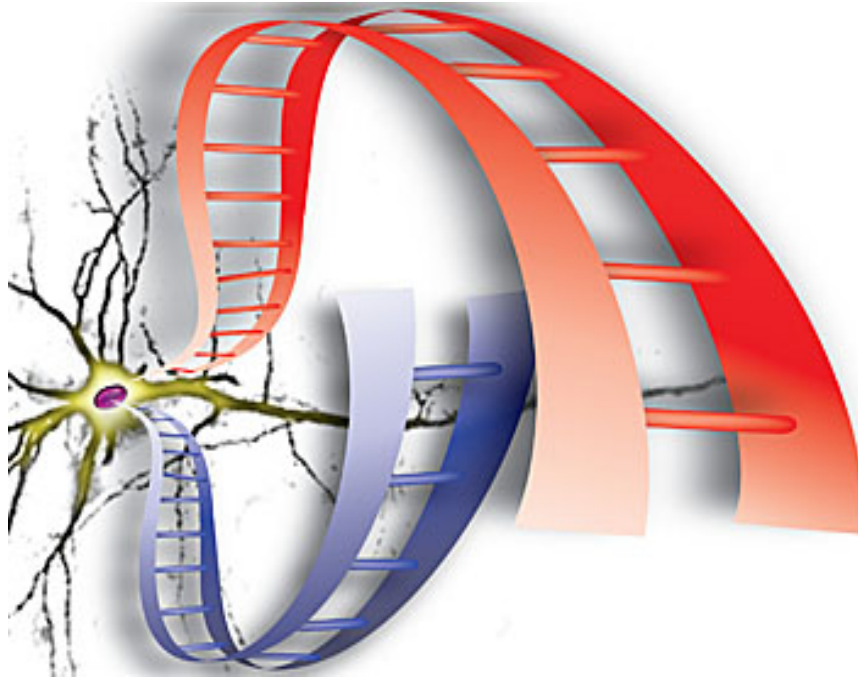


Image Title: The genome is composed of maternally-inherited (red helix) and a paternally-inherited (blue helix) chromosomes. Using a genome-wide deep sequencing approach, researchers have uncovered complex maternal and paternal gene expression programs in the developing and adult brain. - Catherine Dulac and Chris Gregg

Answering the question of how the genetic contributions from mom or dad affect an offspring's behavior just got a lot more complicated. An ambitious new analysis in mice demonstrates that for more than 1,300 genes active in the brain, there is a significant bias as to which copy is active – the one inherited from the mother or the one that came from the father. Furthermore, this bias may shift through the animal's life, and may differ depending on the region of the brain or whether the offspring is male or female.

Most mammalian genes come in pairs, including the roughly 20,000 genes that are active in the brain. One copy is inherited from the father, the other from the mother, and usually both are active together. Thus if a father's copy of a particular gene is defective, the mother's version can at least partly cover for it, and vice versa. But certain genes lack this two-parent harmony: even when both copies are intact the maternal or the paternal copy dominates. This parental bias arises from chemical marks placed on one copy of the gene in a regulatory process called imprinting.

The new findings, reported in two papers that appear in the early online edition of the journal *Science* on July 8, 2010, suggest that imprinting has a significant influence on brain development and behavior. It also likely contributes to diseases of the brain, since imprinting occasionally shuts down the only good gene in a pair.

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- Catherine Dulac

Howard Hughes Medical Institute investigator Catherine Dulac led the team of scientists who conducted the ambitious analysis. Christopher Gregg, a postdoctoral fellow in her Harvard University lab, is the lead author on both of the publications.

"Essentially what we found with these two studies is that imprinting is not only very extensive but also seems to be subject to a lot of regulation, throughout the life of an individual and even according to brain region and gender," says Dulac. "And that makes the phenomenon absolutely fascinating."

Dulac, who has long studied how genes govern behavior, was curious how much of an effect gene imprinting had on the development and function of neural circuits. Researchers had identified less than 100 genes in the mouse brain that were imprinted, but they knew their information was incomplete. A genome-wide survey would be time-consuming and expensive, however, and no one had yet undertaken the project.

Dulac tackled the problem head on, assembling a team of scientists to work together to learn to what extent gene imprinting influences mouse behavior.

With Harvard scientists Bill Carlezon, David Haig, and Naoshige Uchida collaborating with Dulac, the team was well equipped with expertise in mouse genetics, neuroscience, evolutionary theory and motivational behavior. A Collaborative Innovation Award from HHMI ensured funding for all of the team members' contributions to the project.

The two *Science* papers constitute the first step of the study, performed jointly with David Haig, whose expertise in genomic imprinting provided a tremendous asset in the genome-wide characterization of parental bias in the brain, Dulac says. Other aspects of the collaborative project, mainly the functional analysis of genomic imprinting and its role in brain function and disease, are currently underway together with the Uchida and Carlezon teams.

Dulac's team catalogued all the active genes they could find in the brains of 15-day-old mouse embryos, and also in two regions of the brain, the cortex and hypothalamus, in adult mice. The parents of the mice they examined were of two different strains, so that the version of a given gene inherited from the mother was generally easy to distinguish from that supplied by the father. Comparing the sequences of the genes' RNA products in a given mouse to those of the parent mice, Dulac and her colleagues could determine whether the father's or mother's version was significantly more active in the tested tissue.

The 1,308 putative imprinted genes they found represent at least a few percent of the roughly 20,000 genes known to be active in the mouse brain. Just as importantly, the parental bias of many of these genes seemed to be actively regulated rather than permanent. "The set of genes we found to be imprinted in the embryonic brain are different than the set we found to be imprinted in the adult cortex," says Dulac, "and the imprinted genes in the adult cortex are in turn different than the imprinted genes in the preoptic area of the adult hypothalamus."

"The parental effects we uncovered with this approach indicate surprising complexity in the regulation of the transcriptome [the collection of RNA molecules produced by active genes]," says Gregg, noting that the newest DNA sequencing technologies have greatly expanded the kinds of questions researchers are now able to explore.

Another striking finding was that paternal and maternal imprinting isn't evenly mixed: About 60 percent of the imprinted genes in the mouse embryonic brain turned out to be maternal, while about 70 percent of the imprinted genes in the adult brain are paternal. Thus, in early life, it appears that imprinting mostly reflects the mother's influence, and later gives way to the father's. "But the majority of the genes that we found are imprinted during development, which is when mothers have the greatest influence," says Dulac.

In their second paper, Dulac and her team reported that the gene imprinting in an animal can vary depending on whether the animal is male or female. Throughout the genome, they found 347 genes that appeared to be imprinted in adult female mice but not males, or vice versa. This sex-specific imprinting was particularly evident in females in the hypothalamic region of the brain, which mediates maternal and mating behaviors. One example of the complexity they encountered is the gene *Mrp148*, which they found has a paternal expression bias in the hypothalamus of females, but not males.

The studies suggest that embryonic development and post-natal behavior are areas of life in which imprinting has a strong influence. This is broadly consistent with a theory previously proposed by Harvard biologist David Haig, a collaborator on the studies. Haig has pointed out that there are phases of life in which a mother's and father's genes may have an evolutionary "conflict of interest." In a child growing inside his mother's womb, for example, the paternal genes may benefit if the child grows more quickly, while the maternal genes may benefit if the child's growth is more modest, sparing more of the mother's resources for future pregnancies.

"That conflict may be what's generating the phenomenon of genomic imprinting," says Dulac. "It's easy to see how this could be relevant for embryonic development, but it's also plausible that it would affect post-natal brain function too, so that for example the father might want his progeny to suckle for longer, in a way that disadvantages the mother."

A fuller understanding of genomic imprinting should lead not only to further basic science discoveries but also to findings with direct medical relevance. It is already known that some genetic diseases are caused by mutations of imprinted genes, and one of the female-specific imprinted genes Dulac's team detected, *IL-18*, has previously been linked to multiple sclerosis, which predominantly affects women. As the functions of imprinted genes are made clearer, the number of diseases linked to imprinting – and potentially treatable by reversing the imprinting process – seems likely to grow. Sex-specific imprinting could be particularly relevant: "Multiple sclerosis, autism, schizophrenia, anorexia nervosa – these are just a few of the brain diseases that affect more of one sex than another," says Dulac.