Unequal Parenting

MATERNAL AND PATERNAL GENES DON’T ALWAYS HAVE THE SAME EFFECT ON OFFSPRING.

The genes you inherited from your mom and those passed along from your dad don’t have equal footing when it comes to how they influence your biology. Research from a team of HHMI-supported scientists suggests that, throughout an individual’s lifetime, the effect of maternal and paternal genes ebbs and flows in an intricate way.

The interdisciplinary team of scientists—led by HHMI investigator Catherine Dulac of Harvard University, and funded by an HHMI Collaborative Innovation Award—set out to find genes in the mouse brain that had only one activated copy. While mammals have two copies of almost all genes, chemical marks on one of the copies can result in only one being activated.

To find out the frequency of this phenomenon, called imprinting, the researchers bred two genetically distinct species of mice, making it easy to distinguish maternal and paternal genes in the offspring. Then they sampled various sections of the brains of 15-day-old embryos and adults. By sequencing RNA gene products, the scientists could determine whether both copies of that gene were making RNA or whether one copy was muted.

They discovered a whopping 1,308 imprinted genes. What’s more, different genes were imprinted in different regions of the brain, and the patterns of imprinting varied between female and male offspring as well as between embryos and adult mice. About 60 percent of imprinted genes in the mouse embryo brains had the maternal copy turned on and the paternal version stipped. In adult mouse brains, however, about 70 percent of the imprinted genes favored the paternal copy. Almost 350 genes were imprinted in only males or only females. The results appear in two papers published August 6, 2010, in *Science*.

“It’s exciting because it suggests that the maternal and paternal genomes are not providing the same information in the brains of mammals,” says Dulac. “And it affects many, many genes.”

Her team plans to look into whether the imprinting patterns are linked to any diseases. One of the genes that was imprinted only in female mice has been linked to multiple sclerosis, which predominantly affects women. Further research could reveal whether these facts are connected. —SARAH C.P. WILLIAMS

### IN BRIEF

Both research teams found that patterns of gene silencing and activation differed between types of iPS cells depending on their origins. In cells that originated from skin cells, for example, genes for blood cell formation were silenced. And iPS cells derived from blood cells had silenced genes needed to make bone cells.

Daley’s group found that drugs modifying DNA methylation could reset the iPS cells into a more embryonic state, they reported September 16, 2010, in *Nature*. Hochedlinger’s lab group took a different approach to giving the iPS cells a blank slate: they found that growing iPS cells in dishes for a longer period, 3 weeks, cleared the methylation pattern. Those results appeared in the August 2010 issue of *Nature Biotechnology*.

### GETTING TO THE BOTTOM OF CONFETTI SKIN SPOTS

The hallmark appearance of the skin disease “ichthyosis with confetti” (IWC) is bright red skin covering the body, widely speckled with pale, confetti-like spots. The skin disease is rare and doesn’t affect multiple family members, making it hard to track down its genetic cause. But when HHMI investigator Richard Lifton, of Yale University, learned that the pale spots appeared to be normal skin, he had an idea.

Lifton hypothesized that whatever mutation was causing the disease was spontaneously lost in the speckles. So his lab group took 32 biopsies of the confetti spots from different patients and compared them to see if they were missing a similar area of DNA. They were: the same stretch of chromosome 17 was lost in each case.

That made it easier to find the problem in the red, inflamed skin. The researchers went right to chromosome 17 in the inflamed skin cells and found a mutation in the gene *keratin 10*. The mutations varied among individuals, but in all cases they caused the protein product of *keratin 10* to localize to the nuclei of the cell instead of floating free in the cytoplasm. The results of the genetic study appeared online on August 26, 2010, in *Science*.

Next, Lifton’s team hopes to understand why the mutation is lost in so many cells—each patient with the disease has hundreds to thousands of spots of normal skin, and each spot has thousands of healthy cells.

### NEW CLASS OF CANCER-CAUSING MUTATION

A team of researchers studying one type of aggressive ovarian tumor has found that most cases are caused by a gene mutation that broadly regulates DNA activation patterns, linking two fields of research in a novel way.

HHMI investigator Bert Vogelstein and his colleagues at the Johns Hopkins University School of Medicine set out to find genes linked to clear cell ovarian carcinomas, the most treatment-resistant form of ovarian cancer. Their hunt revealed that the majority of these cancers had nearly two dozen mutated genes in each patient. The genes that were mutated varied from tumor to tumor, but four stood out as commonly occurring.

The most commonly mutated gene, *ARID1A*, was altered in 57 percent of the tumors they studied. *ARID1A* caught the researchers’ attention because of its role in defining how cells are epigenetically regulated. Epigenetics refers to the pattern of chemical tags on DNA and histone proteins that regulate which genes are activated and which genes are silenced. Epigenetic attributes can affect the expression of genes but are not part of the DNA sequence itself.

Epigenetic mutations have been found in lung and kidney tumors but only in very rare cases. The *ARID1A* mutations are the first epigenetic mutations to predominate within a class of tumors. The research was published online in *Science Express* on September 8, 2010. Vogelstein hopes the finding will inspire other researchers to look for links between cancer genetics and epigenetics.