

APRIL 30, 2000

Gene Tug-of-War Leads to Distinct Species

By crossing two mouse species that normally do not interbreed, Howard Hughes Medical Institute (HHMI) researchers have gained a better understanding of how gene imprinting can influence the establishment of distinct species.

The majority of mammalian genes are present in two copies that are expressed and regulated. A small number of mammalian genes, however, are subject to special regulation by a process called gene imprinting. The imprint is a chemical mark attached to genes during egg or sperm development. Imprinting physically marks a gene in such a way that the parental origin of the gene can be distinguished and expressed accordingly.

Most imprinted genes seem to govern fetal growth regulation, explained Shirley M. Tilghman, an HHMI investigator at Princeton University. Some researchers speculate that imprinting evolved in order to establish boundaries between species. Imprinting is also thought to provide a barrier to unisexual reproduction and the interbreeding of species.

"We showed that the differences in phenotypes seen in hybrids that are affected by the parent of origin for example overgrown animals versus small really do have something to do with imprinting."

- Paul B. Vrana

An hypothesis about the origin of imprinting, favored by Tilghman and her colleagues, is that imprinting was created as the result of a parental "tug-of-war." According to the theory, fathers contribute genes that enhance growth because their best interests are served if their progeny extract as many maternal resources as possible in order to ensure survival. Mothers, on the other hand, then silence their copy of growth-promoting genes in retaliation because they value all of their progeny equally.

In a research article published in the May 2000 issue of the journal *Nature Genetics*, Tilghman and colleagues at Princeton report that crossing two related mouse species, *Peromyscus polionotus* and *Peromyscus maniculatus*, results in abnormalities in gene imprinting and growth abnormalities in the hybrid offspring.

"We chose these particular species to explore the mechanism of imprinting because Dr. Wally Dawson at the University of South Carolina showed 35 years ago that the abnormal growth seen in the hybrid mice depends on the "direction" of crosses between the two species," said Tilghman. "This suggested to us that the hybrids may have defects in imprinting, and our first idea was that one of the species was not imprinting normally. However, we showed that this was not the case; both species imprint correctly. It is when they hybridize that imprinting goes awry."

Disruptions in growth are thought to contribute to speciation -- the process by which one species gives rise to two others -- because they may reflect a rapidly evolving divergence between species that prevents viable interbreeding. This divergence may be "epigenetic" -- involving easily changeable control elements that alter the expression of genes, but do not affect their DNA sequence.

An epigenetic theory of speciation is attractive to some researchers because the gradual accumulation of genetic mutations that is needed to produce distinct species is considered by some to be too slow to explain the rapid emergence of distinct species.

By conducting a complex series of "backcrosses" between the two *Peromyscus* species and their resulting hybrids, Tilghman and her colleagues sought to determine whether disruption of imprinting affects survival of the offspring.

An analysis of the animals resulting from such backcrosses revealed that the inviability of the hybrids was partly due to two genes -- one on the X chromosome of the *polionotus* species that is expressed only when inherited from the mother, and the other on an autosomal chromosome of the *maniculatus* species that is expressed only when inherited from the father. The scientists localized these genes to two specific regions, or loci, of the mouse chromosomes and found evidence that the two loci directly interacted to create the genetic incompatibility that was reflected in the abnormal growth of the hybrid mice.

The scientists' experimental crosses also revealed that the severity of abnormal overgrowth correlated directly with the disruption of normal imprinting of a number of genes in the animals.

"In other words, the more overgrown the embryos were, the greater the imprinting disruption," said Paul B. Vrana, the article's lead author. "We

found that the two phenomena were highly correlated."

Another important point of this article, Vrana said, is that imprinting signals diverge between species. "We showed that the differences in phenotypes seen in hybrids that are affected by the parent of origin -- for example overgrown animals versus small -- really do have something to do with imprinting."

"In explaining mechanisms of speciation, I believe that people have tended to ignore imprinting, or parent-of-origin effects, simply because until fairly recently we didn't have good genetic explanations for most of them," he said. "However, more explanations of imprinting are now appearing in the literature for both plants and animals. And these are showing that speciation can be produced not only because of incompatible genetic interactions, but also because of epigenetic control of gene expression, like imprinting."