A Genomic Battle of the Sexes

NEWS

Genomic imprinting, which can permit one parent to stifle the genetic contributions of the other, is surprisingly widespread. Why did such a bizarre system evolve?

Shirley Tilghman is no romantic about the relations between the sexes, at least when it comes to genes. "It's a war," the Princeton University developmental biologist announced recently at a public lecture at the National Academy of Sciences in Washington, D.C. No matter how loving a couple may seem, she said, their genes are anything but amicable, and their battleground is the developing embryo. There, in an ongoing molecular battle, "his" genes do what they can to promote their own propagation, and "her" genes fight back to make sure they are not overrun (see Review on p. 2003).

This picture strikes a blow against a basic dogma of biology—that a gene plays the same role in an offspring no matter which parent contributes it, just as Gregor Mendel saw in his pea plants for traits

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The weaker sex. The chromosomes of the smaller, winged male mealy bug are marked and discarded in his son's sperm.

like seed color and plant height. Lately, though, biologists have learned that the sexes have ways to bias genetic inheritance: They can mark particular genes in the set each one contributes so that later—in the germ cells or the new embryo—these genes get special treatment. Still-mysterious biochemical processes can selectively silence the paternal or maternal copies of genes in ways that advance that parent's genetic interests. "It amounts to an outrageous violation of Mendel's rules," says Jon Seger, an evolutionary biologist at the University of Utah, Salt Lake City.

At first glance, imprinting doesn't make much sense, as it seems to undermine some of the hard-won evolutionary advantages of having two sexes in the first place (see p. 1980). For example, a silenced gene no longer offers organisms the safety net of an extra copy of a gene. Imprinting seems even more counterproductive in some insects, where males silence and then discard entire sets of chromosomes. With just one copy of every gene, their offspring have less genetic variety than organisms with two copies of each.

All the same, since the 1930s geneticists have documented imprinting in dozens of insect species. Moreover, mammalian biologists are catching up, identifying dozens of imprinted genes in mammals since independent teams discovered two in 1991. In mammals, imprinted genes have turned out to play key roles in development and, when their expression goes awry, in cancer and genetic disease. And researchers have come up with more than a dozen possible explanations for why this puzzling genetic twist evolved. Many theories circle around the idea of conflict—that, as Tilghman puts it, imprinting is "a battle of the sexes that is fought between the mother and father."

At issue, say many mammalian researchers, is the growth rate of the fetus. About half of the 25 or so mammalian imprinted genes of known function support the notion that fathers contrive to silence genes that rein in growth, boosting the embryo's growth rate and ensuring vigorous offspring. This may run counter to the interests of the mother, who marks and silences growth-promoting genes to keep growth in check. The same seems to be true of a half-dozen genes newly discovered in plants. But not everyone is satisfied with the growth-rate theory. It doesn't seem to apply to all imprinted mammalian genes, and it doesn't explain imprinting in insects. There, imprinting seems to be a struggle between the paternal and maternal genes themselves, battling over which set of chromosomes get passed on, says Seger.

Mother vs. father. Geneticists got their first clues to imprinting about 60 years ago, when Charles Metz, then at the Carnegie Institution of Washington, observed that the sperm in dung gnats somehow deleted chromosomes inherited from the father and passed on only genes contributed by the mother. He concluded that a signature of paternal origin was somehow "impressed," as he called it, on the chromosomes. In plants and mammals, the effects of imprinting are more subtle, as often individual genes rather than whole chromosomes are marked. To date no one knows exactly how imprinting occurs, although methylation of genes is thought to help sustain the imprint in mammals. But although no one knows the mechanism, says Gilean McVean, an evolutionary geneticist at the University of Edinburgh in Scotland, the field has been energized in recent years by new ways to explain imprinting in evolutionary terms.

The growth-rate theory is the brainchild of evolutionary biologist David Haig of Harvard University, who developed it for plants with Mark Westoby in 1989 while at Macquarie University in Sydney, Australia; Tom Moore of the Babraham Institute in Cambridge, U.K., independently came to similar conclusions. The researchers later broadened the ideas to include mammals, and now Tilghman and other mammalian biologists are in their camp.

The researchers realized that when it comes to the growth of offspring, each parent has different interests, particularly in species where the male mates with multiple females and each female invests a great deal of energy in her progeny. The male's interest is in getting the female to invest as much as possible in his offspring—to make each offspring large. She, on the other hand, would be better off rationing her resources to ensure that she can produce additional offspring—likely with different fathers. Thus paternally derived genes would foster large offspring, while maternally derived genes would moderate growth to safeguard the mother. "The selective forces are different," Haig explains.

In animals, Haig predicted that this conflict would be most striking in mammals, where the developing fetus is a virtual parasite on the mother, making some means of control over fetal growth a necessity for her. A few years later, experiments documented imprinting in mammals, and the imprinted genes—growth promoters and inhibitors—"fit right into [Haig's] theory," says McVean.

For example, in 1991, Columbia University researchers found that although the paternal copy of insulin-like growth factor 2 (*Igf2*) was active, the maternal copy of this growth-promoting gene was not. At the same time, a team led by Denise Barlow at the Netherlands Cancer Institute in Amsterdam found that the paternal gene for the Igf2 receptor (*Igf2r*)—a molecule that binds *Igf2* and targets it for destruction—is imprinted and turned off, while the maternal copy is active. Moreover, breeding experiments showed that embryos with no

maternal *Igf2r* genes grew excessively large, while newborns with no paternal *Igf2* were undersized. The same pattern was seen for an imprinted gene called *Gt12*, another growth promoter.

With Haig's idea winning support, Tilghman sought to test it further. The theory implies that monogamous mammals, in which mates' interests are more congruent, should lack imprinting. Tilghman and Paul Vrana, an evolutionary biologist in her lab, found in the literature a set of 1960s experiments in which a monogamous field mouse called *Peromyscus polionotus* was crossed with a closely related polygamous species. If Haig's prediction is correct, a monogamous female crossed with a polygamous male would yield large offspring, because the female would lack the imprinting mechanisms to alter her genes to counteract the male's growth-promoting genes. The opposite cross should yield small mice, as the male wouldn't be able to compensate for the female's growth-inhibiting genes.

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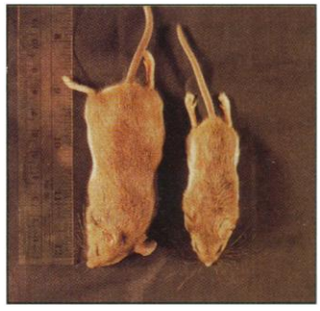
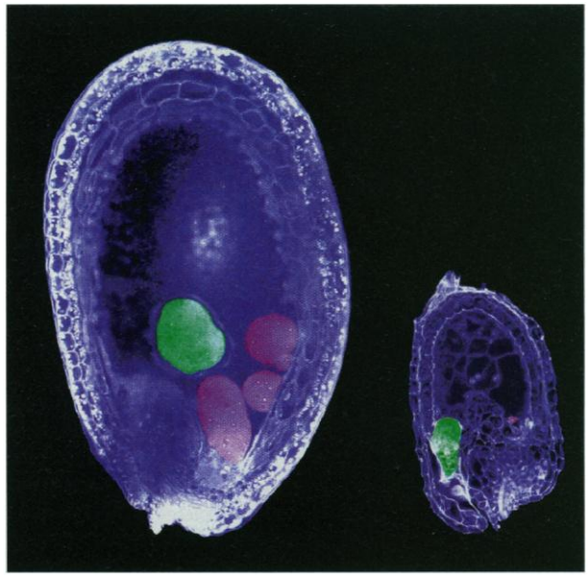


Mighty mouse. Thanks to imprinting, mice with polygamous fathers are large *(left)*, while those with polygamous mothers are small *(right)*.

The results of those earlier experiments and similar ones performed by Vrana and Tilghman, still unpublished, bore out both predictions, Tilghman says (see photo). Whereas newborns from the two species typically weigh 16 to 18 grams, those from the first cross were only about 10 grams and those from the second more than 20 grams. "The [newborn] is so large that it can't be born [properly]," says Tilghman. "And the size differences persisted after birth."

But although these results resoundingly confirmed Haig's growth-rate predictions, his prediction that imprinting would be absent in monogamous species turned out to be false, Tilghman reported in her presentation at the academy. When the team looked at the fate of maternal and paternal genes in the offspring, "to our great surprise, imprinting was working fine in [the monogamous] mouse," she said in her talk. The male genome still turned off known growth-inhibiting genes, such as the *Igf2r* gene, and the female silenced growth-promoting ones, such as *Igf2*.

SCOTT *ET AL.*, *DEVELOPMENT*



Dad's brawn. Imprinting works in plants, too, as seen in these *Arabidopsis* seeds. Those with extra copies of paternal genes grow large *(left)*, but seeds with extra copies from the mother are small *(right)*.

This seems to strike a blow against Haig's ideas on why imprinting exists. But Tilghman reported that the monogamous and polygamous species split apart just 100,000 years ago—perhaps not enough time for imprinting to disappear in the monogamous species.

Indeed, although Haig suggests that imprinting will evolve when the interests of the sexes differ sharply, as in polygamous species, other theorists think it could evolve more easily. For example, evolutionary genetics models by Hamish Spencer from the University of Otago in Dunedin, New Zealand, and his colleagues suggest that multiple paternity isn't a prerequisite for imprinting to be advantageous. "The mathematics suggests it doesn't take much to tip the scales [in favor of imprinting]," says Tilghman. The models indicate that a conflict over growth rate can also pit the mother against her offspring, driving the evolution of imprinted genes.

All for growth? But other evidence indicates that the conflict over fetal growth can't explain all cases of imprinting. Take the male dung gnats whose sperm cells discard paternal chromosomes. In these insects, only one set of chromosomes—from either the mother or the father—winds up in the gamete. So the conflict is not over allocation of the female's resources, but over which genes will be passed on. "If the maternally inherited genes can cause the paternally inherited genes not to be transmitted, they get a twofold boost in fitness," explains Glenn Herrick, a geneticist at the University of Utah, Salt Lake City.

Even in mammals, certain imprinted genes, such as *snrpn*, expressed in the brain, seem to have nothing to do with growth, says evolutionary biologist Laurence Hurst of the University of Bath in the United Kingdom. Furthermore, in 1997, he and McVean surveyed literature on genetic disorders in which a child inherits both copies of one or more chromosome from just one parent and thus gets double doses of paternally or maternally imprinted genes. Multiple copies from the father, rather than leading to bigger babies as Haig would predict, instead led to smaller babies, as did multiple copies from the mother.

Haig explains these results by arguing that normally imprinted male and female genes balance each other out, so when one sex fails to contribute growth can go awry. "It's like a tug-of-war," he says. "If one side drops the rope, you're going to get all sorts of abnormal effects." Hurst and McVean's "evidence doesn't support the model," agrees Tilghman. "But it isn't enough to kill it."

New data from plants are further bolstering the growth-rate hypothesis. In April, Ueli Grossniklaus of Cold Spring Harbor Laboratory in New York and colleagues described what appeared to be an imprinted gene, called *MEDEA*, in the experimental plant *Arabidopsis* (*Science*, 17 April, p. 446). They found that only the maternal copy of *MEDEA* was active and that its normal function was to curb the growth of the embryo.

Likewise, Rod Scott, a plant developmental biologist at the University of Bath, and his colleagues have shown that in general, maternal genomes slow the growth of seeds, while paternal genomes accelerate it. Breeding an *Arabidopsis* plant with four copies of each chromosome with plants carrying the usual two, they created viable offspring with three copies of the genome. If two copies of the genome came from the male, the endosperm (the embryo's nutrient store) and consequently the seed were large; if two copies came from the female, the seed was small, they will report in an upcoming issue of *Development* (see photo). "The results support Haig and Westoby," says Scott.

As far as developmental geneticist Wolf Reik of the Babraham Institute is concerned, Haig's "is the best theory we have right now." And many in the imprinting field agree. Still, given the unexplained cases of this perverse twist of genetics, Haig's explanation isn't likely to be the full story. "These things we call imprinting may be a diverse collection of phenomena with different evolutionary origins," Herrick notes. "But that's not a problem, that's fun." **–ELIZABETH PENNISI**